TITLE: Phase 2 Study of Copanlisib in Combination with Nivolumab in Subjects with Relapsed/Refractory Diffuse Large B-Cell Lymphoma and Primary Mediastinal Large B-Cell Lymphoma

I. Investigator Amendment Request:

Additions in **bold**, deletions are noted as strikethrough

#	Section	Comments
1.	Header	Protocol version date changed to **July 13, 2021**
2.	Title Page	**Amendment 7 / Version 14 / July 13, 2021**
3.	3.2.12	3.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, non-healing wound or ulcer, or bone fracture, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia**, known history of atrial fibrillation except those with 1 event that has resolved more than 1 year ago without recurrence**, or psychiatric illness/social situations that would limit compliance with study requirements.
4.	10.0	f: Perform an evaluation of cardiac function including ECG and echocardiogram **and Troponin** for all patients at screening, and thereafter as clinically indicated. Also perform an evaluation for patients with evidence of CHF, MI, cardiomyopathy, or myositis including lab tests and cardiology consultations including ECG, echocardiogram, CPK and troponin as clinically indicated
5.	4.2.2	4.2.2 Requirements For 10193 Site Registration • IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted) • **Site Initiation Visit** • ETCTN Specimen Tracking Training

NCI Protocol #: 10193
Local Protocol #: MC1787
Protocol Version Date: July 13,, 2021

TITLE: Phase 2 Study of Copanlisib in Combination with Nivolumab in Subjects with Relapsed/Refractory Diffuse Large B-Cell Lymphoma and Primary Mediastinal Large B-Cell Lymphoma

Corresponding Organization: LAO-MA036 / Dana-Farber – Harvard Cancer Center LAO

Principal Investigator: Nora Bennani, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Telephone: (507) 284-2511
Email: bennani.nora@mayo.edu

Co-Investigators: Stephen Ansell, M.D., Ph.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Telephone: (507) 284-2511
Email: ansell.stephen@mayo.edu

Grzegorz S. Nowakowski, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Telephone: (507) 284-2511
Email: Nowakowski.Grzegorz@mayo.edu

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

Statistician
Pamela Atherton, M.S.
Mayo Clinic
Telephone: (507) 284-0660
Email: atherton.pamela@mayo.edu

Project Manager
Katie Gano
Mayo Clinic
Telephone (480) 342-6082
Email: gano.katherine@mayo.edu

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NCI-Supplied Agent(s):

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Nivolumab (NSC 748726)

IND Sponsor: DCTD, NCI.

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Amendment 2 / Version 9/ March 29, 2019
Amendment 3 / Version 10 / August 5, 2019
Amendment 4 / Version 11 / August 3, 2020
Amendment 5 / Version 12 / September 7, 2020
Amendment 6 / Version 13 / February 16, 2021
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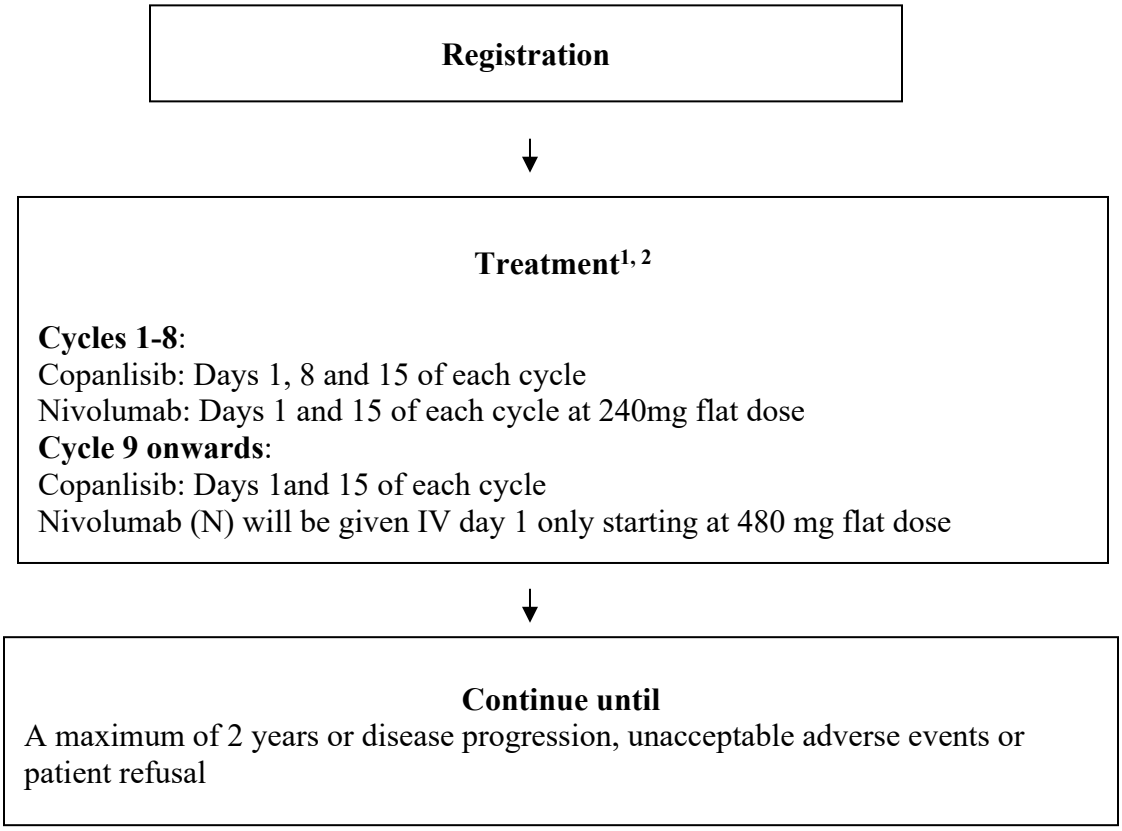
**Protocol types: Original, Revision, or Amendment*

SCHEMA



1. Cycle length = 28 days

2. Copanlisib is to be administered prior to Nivolumab

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1. OBJECTIVES

1.1 Primary Objective

1.1.1 To assess overall response rate (ORR) defined as complete response rate (CR) plus partial response rate (PR) (ORR = CR + PR) of the combination of copanlisib and nivolumab in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL).

1.2 Secondary Objectives

1.2.1 To evaluate the safety of the combination of nivolumab and copanlisib in patients with relapsed/refractory DLBCL and PMBCL.

1.2.2 To determine the progression free survival, duration of response, complete response rate and overall survival of the combination of copanlisib and nivolumab in patients with relapsed or refractory DLBCL and PMBCL.

1.3 Correlative Study Objectives

1.3.1 To characterize the effects of the copanlisib and nivolumab combination regimen on tumor cells, tumor microenvironment and the immune response in relapsed/refractory DLBCL and PMBCL.

1.3.2 To assess predictors of response of the combination in relapsed/refractory DLBCL and PMBCL.

2. BACKGROUND

2.1 DLBCL and PMBCL

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment. The prognosis depends on the histologic type, stage, and response to therapy. The NHLs can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. In Western populations, the majority of NHL (~85%) are of B-cell origin. NHL is a significant medical problem. Last year, the American Cancer Society estimated that 71,850 persons were diagnosed with NHL, and despite recent advances in therapy, 19,790 died from this disease (Siegel et al. 2016). Diffuse large B-cell lymphoma (DLBCL) in itself is recognized to be an aggressive B-cell NHL, often presents clinically in a more symptomatic manner than indolent lymphoma, but a considerable number of these patients can be cured using intensive combination chemotherapy regimens. The standard treatment for patients with aggressive lymphoma who do not obtain a complete response with frontline treatment —or for those who relapse — is intensive salvage

chemotherapy followed by autologous stem cell transplant (ASCT). Not all patients are suitable candidates for this aggressive treatment option. In addition, relapsed or progressive disease after auto-SCT occurs in more than 50% of patients with NHL (Philip et al. 1995); for these patients, prognosis is poor, with a median overall survival of 7 to 11 months (Paltiel et al. 2003). Currently there is no consensus treatment for patients who have relapsed or refractory disease after auto-SCT.

DLBCL is comprised of two major molecular subtypes: germinal center B cell-like (GCB) DLBCL and activated B cell-like (ABC) DLBCL (Alizadeh et al. 2000). All DLBCL lymphomas express the BCR on their cell surface and ABC DLBCLs rely on B-cell receptor (BCR) signaling for their survival. Downstream of the BCR are critical transducers that regulate DLBCL pathogenesis. These include proximal BCR signaling effectors SYK, BTK, BLNK, PLCγ2, PI3Kδ and PKCβ. The pathways downstream of the BCR include the PI3K-AKT-mTOR signaling pathway, which provides a direct conduit from diverse stimuli, including cell surface receptors and metabolic changes within the cell, to downstream pathways affecting cellular growth, size, survival and angiogenesis (Yuan and Cantley 2008). Therefore, the targeting of the PI3K-AKT-mTOR has strong rationale.

Primary mediastinal B-cell lymphoma (PMBCL), originally described in the 1980s, accounts for up to 10% of DLBCL. It is epidemiologically, clinically, and biologically distinct from the other subtypes of DLBCL (GCB]. Similar to nodular sclerosing Hodgkin lymphoma arising in the mediastinum, it is likely derived from a thymic B cell and typically presents in adolescents and young adults with an anterior mediastinal mass, which may invade local structures. Studies of gene expression profiling demonstrate a significant overlap between PMBCL and nodular sclerosing Hodgkin lymphoma. In fact, PMBCL shares a third of its genes with NSHL (Rosenwald et al. 2003). Among the most common genetic alterations in PMBCL are abnormalities on chromosome 9p (up to 75%) and 2p (approximately 50%). Although these abnormalities have been described in NSHL, they are typically not found in the other DLBCL subtypes. The 9p region encodes Janus kinase 2 (JAK2), which then activates the transcription factor signal transducer and activator of transcription (STAT) 6 through phosphorylation (Rosenwald et al. 2003). Also, in the 9p region, programmed death ligands (PD-L) 1 and 2 are rearranged at a frequency of 20% (Twa et al. 2014), which higher than what is seen in other subtypes of DLBCL.

The optimal therapeutic approach to PMBCL is controversial, with a paucity of prospective studies. PMBCL is frequently treated like other DLBCL subtypes. The cure rate for progressive or recurrent disease after primary therapy is low. Across the disease spectrum, relapsed/refractory NHL continues to represent an unmet medical need. Given the few treatment options available for patients with relapsed or refractory lymphoma, novel therapies providing clinical benefit are needed. Treatment with conventional cytotoxic chemotherapy results in promising responses, however a great majority of subjects relapse due to emergence of molecularly resistant clones. Evasion of the host immune responses is an important mechanism for inducing resistance to cancer therapy (Schreiber et al. 2011). Over the last several years, drug development in oncology has seen the emergence of immune therapies. Strategies to block molecular and cellular mediators of cancer induced immunosuppression such as Cytotoxic T-Lymphocyte

Antigen 4 (CTLA4, CD152), Programmed Death -1 receptor (PD-1, CD279) or T regulatory cells (T reg) have been explored both in solid and hematologic malignancies with some success.

Tumor cells up regulate expression of the immune check point receptors (ICR) such as CTLA4, PD-1 and the ligands (PD-L1, B7-H1/CD274) ICR which effectively attenuates the T-cell proliferation and anti-tumor effects. While the necessary machinery for an effective antitumor immune response is present in lymphoma patients, the immune response appears ineffective and most lymphomas escape immune surveillance and progress. In prior work (Wilcox et al. 2009a; Wilcox et al. 2009b; Yang et al. 2012; Yang et al. 2006), we have shown that the tumor microenvironment is highly immunosuppressive due to the presence of regulatory T (Treg) cells, suppressive monocytes and immunosuppressive cytokines. Furthermore, we have found that PD-L1/PD-1 signaling is a dominant mechanism accounting for immune suppression present in the tumor microenvironment (see Figure 1) (Wilcox et al. 2009a; Yang et al. 2012). PD-1 immune check point inhibition has been shown to result in up regulation of genes associated with effector, NK cell function and cytolytic effects (Keir et al. 2008). The cardinal biological effects of PD-1 immune check point inhibition are manifested by reversal of exhaustive CD8+T cells, averting depletion of memory B cells, depleting Foxp3+iTreg cells and restoring robust Th1 immunity (Keir et al. 2008). Targeting PD-1immune check points has the potential to play a major role in cancer therapy by reversing tumor immune escape.

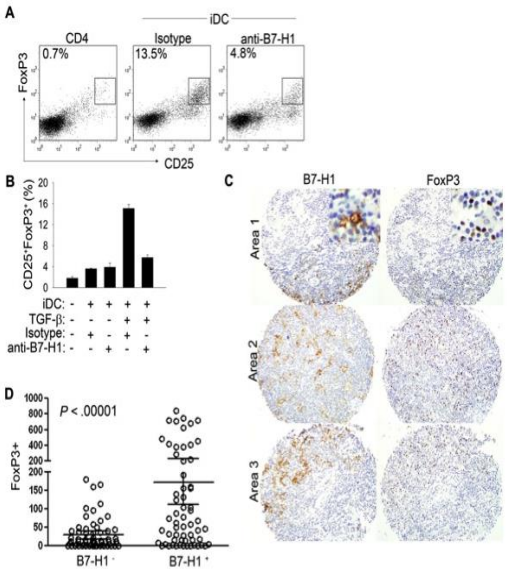

Figure 1: DC-associated PD-L1 promotes the induction of FoxP3$^+$ regulatory T cells. (A-B) Purified CD4$^+$ T cells were depleted of CD25^{hi} natural Tregs and cultured alone or with normal donor monocyte-derived iDCs in triplicate for 6 days. TGF-β (25 ng/mL) was included in the cultures shown in panel A or as indicated. Either an isotype control or blocking anti–PD-L1 (4 μg/mL) antibody was included. The frequency of CD25^{hi}FoxP3$^+$ cells was determined by flow cytometry. Representative dot plots are shown in panel A. Data shown are representative of at least 3 similarly performed experiments. (C-D) Immunohistochemical staining for both PD-L1 and FoxP3 was performed on paraffin-embedded PTCL biopsy specimens (n = 48; in triplicate). PD-L1 and FoxP3 staining from multiple areas of the same biopsy specimen are shown in panel C. (Inset) Original magnification ×200. (D) FoxP3$^+$ cells in each high-power field (± 95% confidence interval is shown) were counted and DC staining for PD-L1 determined. For the purpose of our analysis, core biopsy specimens were considered PD-L1$^+$ if any portion of the specimen contained PD-L1$^+$ DCs.

2.2 CTEP IND Agents

2.2.1 Nivolumab

Nivolumab is a fully human, IgG4(k) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1(B7-H1/CD274) and PD-L2 (B7-DC/CD273), abrogating the inhibitory signals and augmenting host antitumor immune response (Keir et al. 2008). Nivolumab has demonstrated efficacy in solid and hematological malignancies (Ansell et al. 2015; Brahmer et al. 2012). In early phase trials in hematologic malignancies, both nivolumab and pembrolizumab were found to be well tolerated and demonstrated clinical responses in various disease histologies. In Hodgkin lymphoma patients, both agents were highly effective with very durable responses (Ansell et al. 2015). In the nivolumab trial, an analysis of the responses seen in patients with other histological subtypes of lymphoma also showed clinically promising results (Lesokhin et al. 2014). While not quite as impressive as the results seen in the Hodgkin cohort, an overall response rate (ORR) in follicular lymphoma of 40% was seen. In patients with diffuse large B-cell lymphoma, 36% of patients responded to treatment. Though recent unpublished data from a phase 2 trial suggests a much lower ORR in DLBCL, in the low teens. A phase 1b multi-cohort trial in heavily pre-treated relapsed/refractory PMBCL using pembrolizumab showed that it was safe and active in these patients, with an ORR of 41% (7/17) (Zinzani et al. 2017); with a median follow-up of 11.3 months, median duration of response (DOR) was not reached.

2.2.1.1 Nivolumab pharmacokinetics were assessed using a population PK approach, over a dose range of 0.1 to 20 mg/kg administered as a single dose or multiple doses as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks whenadministered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in safety and efficacy between a nivolumab dose of 240 mg or 3 mg/kg every 2 weeks in patients with melanoma, NSCLC, RCC, urothelial carcinoma, MSI-H CRC, and HCC The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age weight, gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

2.2.1.2 Rationale for Modification of the Dosage of Nivolumab After 8 Cycles

Data obtained from manufacturer (Bristol-Myers Squibb) indicates that nivolumab administered as 480 mg Q4W over 30-minutes is expected to offer the same clinical benefit as 3 mg/kg Q2W in subjects with melanoma, squamous non-small cell lung cancer (SQ NSCLC), non-squamous NSCLC (NSQ, NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and classical Hodgkin's lymphoma (cHL). This information is based upon data gathered in the course of the extensive nivolumab development program across multiple tumor types as well as robust clinical pharmacology and quantitative systems pharmacology (QSP) analyses.

The proposed dose modification is based on the comprehensive understanding of nivolumab pharmacology and mechanism of action taken together with the following data and analyses:

- Comparison of nivolumab exposures achieved by 240 mg Q2W, 480 mg Q4W and 3 mg/kg Q2W in subjects with melanoma, NSCLC, RCC, SCCHN, cHL, and UC

- Efficacy bridging evaluation
    - Comparison of the efficacy of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in melanoma, NSCLC, and RCC with respect to the following endpoints: overall survival(OS), objective response (OR)
    - Comparison of predicted receptor occupancy (RO) with nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W, including sensitivity of RO to parameters that may vary across solid tumor types

- Safety bridging evaluation
    - Assessment of safety margins, by comparison of predicted exposures with 240 mg Q2W and 480 mg Q4W relative to the well-tolerated 10 mg/kg Q2W regimen
    - Comparison of the safety of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in subjects with melanoma, SQ and NSQ NSCLC, RCC, SCCHN, cHL, and UC with respect to the following 3 endpoints: Adverse events leading to discontinuation or death (AEDC/D), Grade 3+ adverse events (AE-Grade 3+), and Grade 2+ immune-mediated adverse events (AE-IM Grade 2+)
    - Clinical safety data from subjects treated with nivolumab 480 mg Q4W administered over a 30-minute infusion

The exposure-response efficacy analysis between the 3 mg/kg Q2W and the 480 mg Q4W regimens demonstrated that the hazard ratios for survival with the 480 mg Q4W regimen are very similar to the 3 mg/kg Q2W regimen, resulting in a similar hazard ratio relative to the standard of care treatment studied in each respective phase 3 clinical trial. In addition, these analyses indicated that similar outcomes would be achieved when using an early efficacy measure of response rate (objective response; OR) as well. The exposure-efficacy response trends were consistent across different tumor types with

varying tumor immunogenicity and mutational burdens. Hence, in cases where nivolumab 3 mg/kg Q2W has been proven to be superior to standard of care, nivolumab 480 mg Q4W is predicted to provide comparable benefit, irrespective of tumor type.

This position is further supported by results of the analysis using a mechanistic quantitative systems pharmacology model incorporating transport to site of action, binding kinetics and varied physiological factors representing highly perfused or stromal tumors. The median intratumoral RO predicted with this model is high for nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W trough levels over a range of possible physiological parameter values. It is postulated that high RO at the tumor site will initiate the immuno-stimulatory cascade resulting in similar efficacy with 3 mg/kg Q2W, 240 mgQ2W, and 480 mg Q4W regimens.

Safety bridging was conducted using robust clinical data for the 10 mg/kg Q2W regimen that had a similar safety profile to the 3 mg/kg Q2W regimen. The nivolumab exposure parameters, including Cmax, resulting from 480 mg Q4W were well below Cmaxss values achieved with 10 mg/kg, providing a robust exposure safety margin. In addition, there were negligible differences in the probabilities of experiencing an adverse event irrespective of severity or adverse event type. Moreover, key safety results from the interim safety analysis of CA209511 (Part 2) demonstrate that the safety profile of nivolumab 480 mg IV over 30 minutes Q4W is consistent with the established safety profile of nivolumab (240 mg Q2W or 3 mg/kg Q2W administered IV over 60 minutes) across multiple indications and Summary of Product Characteristics [SmPC]. Taken together, these findings indicated that the safety profile of nivolumab is expected to be unaltered by the proposed dosing regimen changes.

Based on extensive quantitative clinical pharmacology analyses and safety analyses summarized in this submission, the nivolumab 480 mg Q4W regimen administered over 30 minutes is predicted to have similar efficacy and safety profiles to those established with the 3 mg/kg Q2W dosing regimen administered over 60 minutes. Thus, the provided analyses support the proposed nivolumab dosing regimen of 480 mg Q4W administered over 30 minutes as a convenient treatment option.

Based on this information the dosage of Nivolumab will be 240 mg IV every 2 weeks for the first 8 cycles on the study. After 8 cycles, Nivolumab will be administered at the dose of 480 mg IV every 4 weeks. Both dosage strengths will be infused over 30 minutes.

2.2.2 Copanlisib (BAY 80-6946)

The B-cell receptor (BCR) signaling pathway is critical for the development, proliferation, and survival of malignant B-cells. Drugs targeting BCR pathway kinases, including the Bruton's tyrosine kinase inhibitor ibrutinib [2] and the phosphatidylinositol 3-kinase (PI3K)-δ isoform inhibitor idelalisib [3], have proven to be effective treatment options in patients who have relapsed or are refractory to standard therapy. However, fatal and/or serious toxicities have been associated with idelalisib use [3, 4] and, recently,

frequent serious adverse events, including hepatic and gastrointestinal toxicity, colitis, opportunistic infections, autoimmune toxicities, and pneumonitis, have raised safety concerns around idelalisib in combination with standard therapies [5–7]. Therefore, new approaches, such as dual inhibition of PI3K-δ and PI3K-α, are necessary to both mitigate toxicity issues and improve efficacy [8–10].

Copanlisib (BAY 80-6946; Bayer AG, Berlin, Germany) is an intravenous pan-class I PI3K inhibitor with predominant activity against the PI3K-α and PI3K-δ isoform (Liu et al. 2013). A first-inhuman phase 1 study established the maximum tolerated dose of copanlisib as 0.8 mg/kg administered on days 1, 8, and 15 of a 28-day cycle (Patnaik et al. 2016). In an expansion cohort including NHL patients, severe toxicities were low and there were early signs of efficacy, including complete response (CR) or partial response (PR) in all six patients with relapsed or refractory follicular lymphoma, and one of three patients with DLBCL (Patnaik et al. 2016). A phase 2 study of copanlisib conducted in indolent and aggressive lymphomas (Dreyling et al. 2017), the ORR was 43.7% (14/32) in the indolent cohort and 27.1% (13/48) in the aggressive cohort including mantle cell lymphoma, Peripheral T-cell lymphoma and DLBCL; median progression-free survival (PFS) was 70 days (range, 0–897) in the aggressive cohort with a median DOR of 166 days (range, 0–786). In the 15 patient with DLBCL out of a total of 34 patients with aggressive lymphomas, only 1 PR was seen with an ORR of 6.7%, Common adverse events included hyperglycemia (57.1%; grade ≥ 3, 23.8%), hypertension (54.8%; grade ≥ 3, 40.5%), and diarrhea (40.5%; grade ≥ 3, 4.8%), all generally manageable. Neutropenia occurred in 28.6% of patients (grade 4, 11.9%) (Dreyling et al. 2017). In a phase 2 study of 40 patients with relapsed/refractory DLBCL after 1 or more lines of therapy, the ORR was 25%. Higher responses were seen in the ABC subtype (37.5%) as compared to the GCB subgroup (13.6%) (Lenz et al. 2017). To date, there is no data with copanlisib in PMBCL.

Copanlisib Pharmacokinetics:

Copanlisib demonstrated dose-proportional increases in the plasma exposures (Cmax and [AUC(0 25)] over the dose range of 0.1 to 1.2 mg/kg (absolute dose range: 5 to 93 mg) with a terminal elimination half-life of 39.1 h. There is no time-dependency and no accumulation in the pharmacokinetics of copanlisib. The recommended (Phase 2) and approved dose of monotherapy copanlisib is 60 mg given i.v. as a one hour IV infusion on an intermittent weekly schedule on days 1, 8 and 15 in a 3 weeks on/1 week off schedule.

Copanlisib is eliminated predominantly via feces (64%; unchanged 30%) compared to urine (22%; unchanged 15%). Population pharmacokinetic analyses showed that age, gender, race, smoking status, body weight, mild hepatic impairment, and mild to moderate renal impairment had no clinically significant effect on the pharmacokinetics of copanlisib and therefore no dose recommendation is needed for these specific populations. Based on the preliminary categorical analyses and the central tendency, copanlisib does not prolong the QT/QTc interval.

Copanlisib metabolism is primarily mediated by CYP3A (>90%) with minor contribution

of CYP1A1 (<10%). Concomitant use of copanlisib with strong cytochrome P450 3A (CYP3A) inducers may decrease copanlisib AUC and should be avoided. Concomitant use of copanlisib with strong CYP3A inhibitors increases copanlisib AUC and a dosage reduction to 45 mg is advised if patients required strong inhibitors. Copanlisib has low risk for clinical drug-drug interactions of concomitant drug products through inhibition or induction of CYP enzymes, inhibition of uridine diphosphate glucuronosyltransferase (UGT) enzymes. Copanlisib is not an inhibitor of P-gp, BCRP, multi-drug resistance-associated protein (MRP2), bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT 1, OAT3, OCT1, OCT2, and MATE1 at therapeutic 60 mg dose plasma concentrations. Copanlisib is an inhibitor of MATE2-K at therapeutic 60 mg dose plasma concentrations.

Further details can be found in the latest available version of the investigator's brochure (2017), Which contains comprehensive information on the study drug and the United States Package Insert (USPI).

2.3 Rationale for Combination

In a preclinical mouse model, p110δ inactivation in regulatory T cells (Treg) unleashes CD8+ cytotoxic T cells and induces tumor regression (Ali et al. 2014). Thus, p110δ inhibitors can break tumor-induced immune tolerance. In the A20 DLBCL syngeneic mouse model with tumor intrinsic regulation of the immunosuppressive environment, treatment with copanlisib resulted in effective down regulation of tumor-infiltrating Tregs and an increase of INFg+ CD44+ cells in tumors (Liu 2017). PR were observed in 75% of mice treated with copanlisib in combination with a surrogate anti-mouse PD-1 (aPD-1, BioXCell) compared to 0% PR in the monotherapy groups. These data support the rational for the combination of copanlisib and nivolumab in DLBCL.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have a histopathologically confirmed diagnosis of diffuse large B-cell lymphoma (DBLCL) or primary mediastinal large B-cell lymphoma.

3.1.2 Patients must have measurable disease, defined as at least one lesion that is ≥ 15 mm (≥ 1.5 cm) in the longest axis on cross-sectional imaging and measurable in two perpendicular dimensions per spiral CT scan or PET-CT scan.

3.1.3 Patients must have disease that is recurrent or refractory to standard therapy. Patients must have failed front-line therapy and declined or are not candidates for autologous stem cell transplant (ASCT) or have failed prior ASCT.

3.1.4 Age ≥ 18 years.
Because no dosing or adverse event data are currently available on the use of copanlisib and nivolumab combination in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials. However, if pediatric colleagues and centers are interested in including patients ages 12 to 18 in this trial, this trial then could be available to this group of patients.

3.1.5 ECOG performance status of 0, 1 or 2 (See Appendix A).

3.1.6 Life expectancy of greater than 12 weeks

3.1.7 Patients must have normal organ and marrow function as defined below:

- White blood cell (WBC) ≥ 2000/mm^3
- Absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin > 9.0 g/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
- Aspartate transaminase (AST) ≤ 2.5 x ULN
- Serum creatinine ≤ 2.0 mg/dL
  OR
- Calculated creatinine clearance (CrCl) ≥ 30 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dL}}$$

3.1.8 Negative urine or serum pregnancy test for females of child bearing potential within 7 days prior to registration.

The effects of copanlisib and nivolumab on the developing human fetus are unknown. For this reason, and because the study drugs used in this trial are known to be teratogenic, females of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and for *5 months* after the last dose of study drug. Males who are the sexual partners of a female of child-bearing potential must use any contraceptive method with a failure rate of less than 1% per year for the duration of study participation and for a period of *7 months* after the last dose of study drug. These periods of required use of contraception have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that females of child-bearing potential use contraception for 5 months and males who are the sexual partners of females of child-bearing potential use contraception for 7 months.

Females must not breast-feeding for 1 month after last dose.

Females of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab.

A female of child-bearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a female over 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

Females who are not of childbearing potential (*i.e.*, who are postmenopausal or surgically sterile) and azoospermic males do not require contraception.

Should a female of child-bearing potential become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) should inform the treating physician immediately.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Any high grade B-cell lymphoma

3.2.2 Patients who have had chemotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C), anticancer antibodies within 4 weeks, radio or toxin immunoconjugates within 2 weeks, radiation therapy within 3 weeks or major surgery within 2 weeks prior to entering the study.

Palliative (limited-field) radiation therapy is permitted if the patient has additional measurable lesions to assess response of therapy.

3.2.3 Patients who have not recovered to grade 1 or less from any adverse events due to agents administered more than 4 weeks earlier (excluding alopecia).

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Patients should be excluded if they have had prior treatment with a Pi3 kinase inhibitor, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways. *Note:* Patients who previously received CART therapy and progressed will be eligible.

3.2.6 Patients who have received autologous stem cell transplant (ASCT) ≤ 8 weeks prior to the first dose of study drug or no adequate count recovery.

3.2.7 Patients with a prior history of allogeneic stem cell or solid organ transplantation.

3.2.8 Patients with evidence of active disease in the central nervous system (CNS) defined as either the presence of active lesions on MRI obtained within 4 weeks of registration or progressive neurological decline.

Patients with primary CNS lymphoma who develop systemic recurrence following standard therapy may be included as long as no active CNS disease is present at the time or enrollment. Similarly, patients with secondary involvement of the CNS from a systemic lymphoma may be included as long as the CNS disease has been optimally treated and they demonstrate no evidence of active CNS disease.

3.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to copanlisib and/or nivolumab.

3.2.10 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.11 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, non-healing wound or ulcer, or bone fracture, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, known history of atrial fibrillation except those with 1 event that has resolved more than 1 year ago without recurrence, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.13 Pregnant women are excluded from this study because copanlisib and nivolumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with copanlisib or nivolumab, breastfeeding should be discontinued for 1 month after last dose if the mother is treated with copanlisib or nivolumab.

3.2.14 Patients with human immunodeficiency virus (HIV):
Patients with human immunodeficiency virus (HIV) are eligible for the study provided they meet the other protocol criteria in addition to the following:

- Undetectable HIV load by standard PCR clinical assay
- Absolute CD4 count of ≥ 200 mm^3
- Willing to maintain adherence to combination antiretroviral therapy
- No history of AIDS defining condition (other than lymphoma or CD4 cell count < 200 mm^3)
- Likely to have near normal lifespan if not for the presence of relapsed/refractory lymphoma

The Patients with evidence of HBV are eligible provided there is minimal hepatic injury and the patient has undetectable HBV on suppressive HBV therapy. Patient must be willing to maintain adherence to HBV therapy.

Patients with previously treated and eradicated HCV who have minimal hepatic injury are eligible.

3.2.15 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.2.16 Patients are permitted to enroll if they have vitiligo, type 1 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 (precipitating event). However, Patients with uncontrolled Type I or II diabetes mellitus will be excluded; uncontrolled diabetes is defined as HbA1c >8.5%.

3.2.17 Patients should be excluded if they have a 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 $\leq$ 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if $\leq$ 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (*e.g.*, contrast dye allergy) or for treatment of non-autoimmune conditions (*e.g.*, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

3.2.18 Patients who have had evidence of active or acute diverticulitis, intra-abdominal abscess, and GI obstruction which are known risk factors for bowel perforation should be evaluated for the potential need for additional treatment before coming on study.

3.2.19 Patients with other active malignancy $\leq$ 3 years prior to registration for which active treatment is required must be excluded. Patients with composite lymphomas that have a non-B-cell component must be excluded.
EXCEPTIONS: Non-melanotic skin cancers or carcinoma-in-situ of the cervix.

3.2.20 Copanlisib is primarily metabolized by CYP3A4. Therefore, the concomitant use of strong inhibitors of CYP3A4 (*e.g.*, ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of CYP3A4 (*e.g.* rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted from 14 days prior to enrollment until the end of the study.
Note: Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. APPENDIX B (Patient Drug Information Handout and Wallet Card) should be provided to patients. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.
Other medications that are prohibited while on copanlisib treatment:

- Herbal medications/preparations (except for vitamins)
- Anti-arrhythmic therapy other than beta blockers or digoxin

For the list of specific medications prohibited while on copanlisib treatment refer to the APPENDIX B).

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

This study will be available to all eligible patients regardless of race or ethnic group.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation

requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number

- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10193 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MN026 and protocol 10193.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10193 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Site Initiation Visit
- ETCTN Specimen Tracking Training

- All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
- Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
- The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking system may require new training.
- This training will need to be completed before first/further patient enrollment at a given site.
- Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and DVulih@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and

institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Registration

4.2.5 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.2.6 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form.

4.2.7 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3 General Guidelines

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. The study drugs will be administered in sequence, copanlisib must be administered before nivolumab. Do not administer study drugs concurrently. For patients receiving both drugs, the intravenous catheter must be flushed with 0.9% sodium chloride between the two infusions. Pre-medication is not needed unless a patient develops an infusion reaction.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Copanlisib

Copanlisib is administered by the 1 hour IV infusion weekly for 3 weeks (days 1, 8, and 15) of each 28-day cycle. Copanlisib dose will be determined using a safety cohort in 6 patients with Copanlisib 60 mg weekly days 1,8,15 with Nivolumab 240 mg IV on days 1 and 15 each cycle. Copanlisib could be reduced to 45 mg if toxicity was observed with the combination, and the safety cohort will be re-evaluated (Investigator's Brochure, 2016). Cycle 9 and beyond treatment will be given as follows: Copanlisib: Days 1and 15 of each cycle Nivolumab (N) will be given IV day 1 only starting at 480 mg flat dose.

Cycle 1, Day 1 (C1D1)

The following assessments should be performed on Cycle 1, Day 1 before receiving study treatment unless otherwise specified.

- On Cycle 1 Day 1, patients are not required to be fasting prior to the pre-dose glucose measurement.

- Glucose will be measured at pre-dose and post dose 1 hour and 2 hours after the end of copanlisib infusion, (window of ± 10 min is allowed except for the pre-dose measurement). Additional measurements to be performed at the clinic as clinically indicated.

NOTE: If patient needs to take a meal, then glucose test should be take prior to meal intake.

Subsequent visits after C1D1 visit

Fasting is not required prior to pre-dose glucose measurement.

- Glucose will be measured at pre-dose and post dose 1 hour after the end of copanlisib infusion (window of ± 10 min is allowed except for the pre-dose measurement). Additional measurements to be performed at the clinic as clinically indicated.

- Review of the blood glucose measurements/meal timing/insulin administration/oral glucose lowering medication, if applicable.
- Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.

The requirements for fasting and pre-dose glucose levels are presented in Table 5.1.

Table 5.1 Fasting requirements and pre-dose glucose levels

Period	Fasting ≥ 8 h required before first glucose measurement	Pre-dose glucose levels (first glucose measurement)
Day 1 of cycle 1	No [a]	≤160 mg/dL (fasting) <200 mg/dL (non-fasting)
Subsequent infusions after Cycle 1 Day 1	No [b]	<160 mg/dL (fasting) < 200 mg/dL (non-fasting)

a: Diabetic patients who take insulin treatment at any cycle visit:
Timing and content of meal intake will be managed by the investigator. Consultation with treating physician or diabetes/endocrinologist is advised.

b: The decision regarding meal timing and fasting can be made by the investigator based on glucose response patterns during prior treatment days

- Fasting refers to a ≥ 8 h fast.
- Non-fasting status includes any caloric intake such as meals and also juice, snacks, and other caloric intake not consistently called a meal.

From Cycle 1 Day 1 onwards, glucose measurements at the site may be done either by laboratory analysis or in capillary blood.

Because of inhibitory effect on PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporarily increase in blood glucose. Addition of meal in close proximity to copanlisib infusion may exacerbate glucose increase.

On infusion days, a low carbohydrate diet is recommended, the timing and content of caloric meal intake and additional glucose testing (if clinically indicated) is managed and monitored by the investigators based on glucose response patterns during prior treatment days.

All glucose measurements done at the site, oral glucose lowering medication and/or insulin administration, if applicable, fasting/non-fasting status and meal intake timing on infusion days will be collected as part of the clinical source documentation.

The use of corticosteroids as antiemetics prior to copanlisib administration is not allowed. After administration, flush the line with 0.9 % sodium chloride to ensure complete dose is given. No IV glucose preparations should be administered on the days of infusion.

5.1.2 Nivolumab

Nivolumab will be given intravenously at a dose of 240 mg on days 1 and 15 of each 28-day cycle for cycles 1 through 8 and at a dose of 480 mg on day 1 of cycle 9 and all subsequent cycles.

Nivolumab is to be administered as a 30-minute IV infusion, using a volumetric pump with a 0.2-1.2 micron in-line filter at the protocol-specified dose. Fixed dose (eg, 240 mg, 360 mg, or 480 mg flat dose) nivolumab injection can be infused undiluted or diluted with 0.9% normal saline so as not to exceed a total infusion volume of 160 mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

5.1.3 Safety Cohort

No dose escalation will be utilized, but a safety run-in of 6 patients with DLBCL or PLBCL will be enrolled to evaluate the safety of the treatment combination. Patients will be enrolled to receive 60 mg of Copanlisib and 240 mg IV of Nivolumab as per the dose schedule in Table 5.1.3

Table 5.1.3

Dose level	Copanlisib	Nivolumab**
-2	45 mg Days 1 and 15	240 mg IV Days 1 and 15
-1	60 mg Days 1 and 15	240 mg IV Days 1 and 15
*1	60 mg Days 1, 8, 15	240 mg IV Days 1 and 15

*safety run-in dose level
**480mg on day 1 only cycle 9 and beyond

Copanlisib: Given IV on days 1, 8 and 15 during every 28-day cycle for cycles 1-8. Cycle 9 and beyond, IV will be given on days 1 and 15

Nivolumab: All patients: 240 mg given IV on days 1 and 15 for cycles 1 through 8 followed by 480 mg on day 1 only of all subsequent cycles thereafter

5.1.3.1 Six patients will be treated at the planned dose and observed for a minimum of 28 days before accruing the rest of the patients. If no DLTs are observed (as per section 5.24) the study will open to complete accrual. If at least 2 of 6 patients experience a DLT, then 6 patients will be accrued at the -1 dose level and observed for a minimum of 28 days. If at least 2 of 6 patients at the -1 dose level experience a DLT, this study will cease accrual. If 1 or less patients experience a DLT at the -1 dose level, the study will open to complete accrual. If 1 or less patients experience DLTs at dose level 1, the study will open to complete accrual.

5.1.3.3 Definitions of DLT

A DLT is defined by the occurrence of any of the following toxicities (CTCAE v.5) within the first cycle of treatment of dose escalation cohorts, which is possibly, probably, or definitely related to copanlisib and/or nivolumab in order to evaluate potential toxicity related treatment delays or any event within the first cycle of treatment that requires permanent discontinuation of copanlisib, and/or nivolumab.

5.1.3.3.1 Non-Hematological DLT

Any Grade 3 or Grade 4 non-hematological toxicity that is possibly, probably or definitely attributable to the treatment regimen is considered a DLT, including the following:

- Non-hematologic toxicity that causes a delay of >14 days in initiating cycle 2.
- Any type of grade 3-4 hypersensitivity reaction (i.e.: allergic reaction, anaphylaxis, serum sickness, skin disorders, etc.), regardless of attribution, that necessitate discontinuation of study drug.
- Any type of grade 3-4 immune related adverse event including skin reactions.
- Grade 3 or greater colitis and bowel perforation
- Grade 3 ALT/AST elevation or 10 x ULN
- Grade 3-4 pneumonitis
- Grade 4 hyperglycemia: persistent post-infusion grade 4 hyperglycemia despite optimal glucose lowering therapy in consultation with an endocrinologist. Definition of persistent occurrence is based on repeated fasting blood glucose measurement following treatment with copanlisib.

5.1.3.3.2 The following events are exclusions and are NOT considered a DLT for this protocol,

regardless of attribution or specific type:
  - Grade 3 nausea, vomiting, diarrhea, or oral mucositis with < 3 days duration
  - Grade 3 fever
  - Grade 3 infection
  - Grade 3 peripheral sensory neuropathy that is decreased by at least one grade within 7 days
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive (i.e.: decreased by at least one grade) to oral supplementation within 7 days
  - Grade 3 hypertriglyceridemia that returns to < Grade 2 prior to the beginning of cycle 2
- Grade 3 hyperglycemia that returns to < Grade 2 (with or without the use of insulin or oral diabetic agents) prior to the beginning of cycle 2. Transient infusion-related hyperglycemia lasting < 7 days are also excluded.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of copanlisib and nivolumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The known potential targets for drug interaction are CYP3A4 inducers or inhibitors, as well as drugs modulating MATE2K function. **APPENDIX B** (Patient Drug Information Handout and Wallet Card) should be provided to patients.

- Sensitive substrates of the renal drug transporter MATE2K (*e.g*. metformin) need to be used with caution. Metformin should be interrupted for 48 hours after receiving iodinated contrast media. Please see prescribing information for further information.
- Patients taking medications with narrow therapeutic index should be proactively monitored if these medications cannot be avoided. These medications may include quinidine, cyclosporine, and digoxin.
- Systemic corticosteroid therapy at a daily dose higher than 10 mg prednisone or equivalent is not permitted while on study. Previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days prior to the CT/MRI screening. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening. Patients may be using topical or inhaled corticosteroids. Short-term (up to 7 days) systemic corticosteroids above 10 mg prednisolone or equivalent will be allowed for the management of acute conditions (*e.g*., treatment non-infectious pneumonitis). The use of corticosteroids as antiemetics prior to copanlisib administration will not be allowed.
- Patients should stop using herbal medications at least 7 days prior to the first dose of copanlisib. Herbal medications include, but are not limited to: St. John’s Wort,

Kava, ephedra, gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng.

- Patients with NHL, particularly after several lines of therapy are at risk for opportunistic infections. Patients will be monitored symptomatically very closely at every visit prior to each cycle. If any symptoms were to arise suggestive of an opportunistic infection, evaluation guided by the presenting symptom will be initiated immediately such as chest X-ray, CT scan of the chest and bronchoscopy if needed. Appropriate supportive care measures and antibiotic coverage will be started.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for a maximum of 2 years or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.4 Duration of Follow Up

Patients will be followed for 100 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6. Dosing Delays/Dose Modifications for Copanlisib and Nivolumab

Below are dose modification tables applicable to all patients participating in this study for the following adverse events.

Patients who develop adverse events while being treated must have one or both drugs held or discontinued according to the guidance provided in the tables below.

Please use as written and contact the drug monitor for any proposed changes. Note that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended treatment modification for the most serious event that has a higher level of modification, i.e. going off study treatment versus holding drug.

Dose hold = study drugs must be held as indicated. Day 1 of the next cycle is given when the patient meets the protocol criteria to restart drugs. The current cycle will include all days until the patient resumes treatment and may be longer than 28 days.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
≤ Grade 1	No change in dose *	NA
Grade 2	Hold* until 1≤ Grade resolved (#). Resume at same dose level.	NA
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion	NA
Grade 4	Off protocol therapy	NA
	*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no	NA

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
	associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines		

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
≤ Grade 1	Hold until UNL or baseline #. Resume at same dose level.	Continue therapy
Grade 2	Hold until UNL or baseline. Resume at same dose level.	Hold until UNL or baseline. Resume using alternative dosing schedule at 60 mg on D1, and D15
Grade 3	Off nivolumab therapy	Hold until Grade≤1. Resume at 45 mg dose on D1 and D15. If a dose reduction beyond 45 mg on D1 and 15 of each cycle is required, copanlisib will be discontinued
Grade 4	Off protocol therapy	Off Protocol
	Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatic AE management algorithm		

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
≤ Grade 1	Hold until baseline #. No change in dose	No change in dose
Grade 2	Hold until baseline. No change in	Hold until baseline, then resume using

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
	dose	alternative dosing schedule at 60 mg on D1, and D15
Grade 3	Off protocol therapy.	Hold* until < Grade 2. Resume at one dose level lower, 45 mg dose given on D1 and D15.**
Grade 4	Off protocol therapy	Off protocol therapy
	See GI AE Algorithm for management of symptomatic colitis. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	*Patients requiring a delay of >2 weeks should go off protocol therapy. ** Patients requiring a dose reduction beyond 45 mg on D1 and 15 of each cycle, copanlisib will be discontinued. Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.
Recommended management: see GI AE management Algorithm		

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
≤ Grade 1	Hold until baseline. Resume at same dose level if asymptomatic	No change in dose
Grade 2	Hold until baseline. Resume at same dose level if asymptomatic	Hold until baseline. Resume at same dose level if asymptomatic
Grade 3	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be	Hold until Grade 1 or less. Resume at 60mg D1 and D15

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
	taken off treatment	
Grade 4	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment	Off protocol therapy
	Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm	

Pneumonitis	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis.	No Change
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes nivolumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required. ^	Dose Interruption Until recovery to ≤grade 1.Resume at 45mg D1 and D15. No re-escalation allowed after this dose reduction. If second recurrence, permanent

Pneumonitis	**Management/Next Dose for Nivolumab**	**Management/Next Dose For Copanlisib**
		discontinuation.
Grade 3	Hold dose pending evaluation. Resume without change in dose after pulmonary and/or ID consultation excludes nivolumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required	Hold dose pending evaluation. If non-infectious pneumonitis excluded, may resume until grade ≤1 at 45mg D1 and D15. No re-escalation allowed after this dose reduction. If second recurrence, permanent discontinuation. Discontinue if proven non-infectious pneumonitis.
Grade 4	Off protocol therapy	Permanent Discontinuation
	Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	The investigator is requested to differentiate between non-infectious pneumonitis, and infectious pneumonitis (viral, bacterial, or fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion; and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".
Recommended management: See Pulmonary Adverse Event Management Algorithm		

Nausea/Vomiting	**Management/Next Dose for [Nivolumab]**	**Management/Next Dose for [copanlisib]**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1 or baseline. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Off protocol	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		

Nausea/Vomiting	**Management/Next Dose for [Nivolumab]**	**Management/Next Dose for [copanlisib]**
Recommended management: antiemetics.		

Nivolumab:

Please refer to the Nivolumab Investigator Brochure or Appendix C to the protocol for toxicity management algorithms which include specific treatment guidelines. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study PI or drug monitor is recommended.

In several places there are differences from the algorithms regarding protocol directed drug modifications and these are identified with (#). In these cases please follow the protocol specific guidelines in this section.

Generally we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines.

ALL OTHER EVENTS	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below)
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy
Recommended management: As clinically indicated	

- Any grade 2 drug-related uveitis or eye pain 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 should go off protocol treatment

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

- Lymphopenia is an expected event for both study drugs. Asymptomatic lymphopenia does not constitute reason to hold or discontinue the study drugs, regardless of the grade

Other GI (not Nausea and Vomiting)	**Management/Next Dose**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy.
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose**
≤ Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation	

Neurologic events	**Management/Next Dose**
≤ Grade 1	Hold dose pending evaluation and observation (#). Resume with no change in dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. (#) Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy)^
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy.
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome and myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose**
≤ Grade 1	Asymptomatic TSH elevation.* Continue therapy.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks. Resume at same dose level. Endocrine consult recommended
Grade 3	Off study treatment.
Grade 4	Off protocol therapy.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Endocrine Management Algorithm	

Renal	**Management/Next Dose**
≤ Grade 1	No change in dose. Monitor toxicity weekly until returned to baseline.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment.
Recommended management: See Renal Management Algorithm	

Infusion reaction	**Management/Next Dose**
≤ Grade 1	Infusion rate may be slowed or interrupted and restarted 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 patient closely. See Section 5.7 for details on management of Infusion Reactions.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	

Fever	**Management/Next Dose**
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.

Fever	**Management/Next Dose**
Grade 4	Off treatment.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
See section 5. infusion reactions	

Cardiac *	**Management/Next Dose for Nivolumab** **Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off treatment.
* Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin **Patients with evidence of myositis without myocarditis may be treated according as "other event" Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

- Drug will be held for grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

If treatment is delayed > 6 weeks for an adverse event, the patient must be permanently discontinued from study therapy.

Patients requiring high dose steroid treatment for autoimmune or inflammatory events should go off study treatment except for a short course of tapering steroids for infusion reaction, skin rash or endocrine events.

Patients with grade 3 thyroiditis and skin rash may continue therapy with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.

Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.
Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment.

Patients requiring > two dose delays for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results.
Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

Copanlisib:

Neutropenia	**Management/Next Dose for Copanlisib**
≤ Grade 1 ANC≤1500/mm^3	No change in dose
Grade 2 ANC<1500-1000/mm^3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3 ANC<1000-500/mm^3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4 ANC<500/mm^3	Off protocol therapy.

Neutropenia	**Management/Next Dose for Copanlisib**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Thrombocytopenia Platelet counts	**Management/Next Dose for Copanlisib**
≤ Grade 1 ≤ 75'000/mm^3	No change in dose
Grade 2 <75'000-50'000/mm^3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3 <50'000-25'000/mm^3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4 <25'000/mm^3	Off protocol therapy.

6.1 Dose Modification rules for transient post-infusion hyperglycemia

Patients who develop transient post-infusion glucose>250 mg/dL after study drug administration may continue treatment. However, the next infusion must be delayed until the patient's pre-infusion glucose levels return to <160 mg/dL (fasting) or <200 mg/dL (non-fasting). Guidelines for the management of transient glucose increases are given in APPENDIX D and APPENDIX E. Continuing occurrence of post-infusion blood glucose >400 mg/dL, based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of copanlisib, will require dose reduction by one dose level.

- Further dose reduction **(where appropriate per study design/population)** is allowed as long as discontinuation criteria was not met.
- Dose re-escalation is allowed when a patient has achieved controlled glucose levels per investigator's judgment.
- Persistent occurrence of post-infusion blood glucose >400 mg/dL based on laboratory analysis which occurred at the lowest dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist requires permanent discontinuation of the study drug.

6.2 Treatment of blood pressure increases associated with copanlisib

It is important that patients with pre-existing arterial hypertension adhere to their regular medication schedule and take their usual doses on the days of study drug infusion.

The management of acute blood pressure (BP) increases following copanlisib will need to be individualized for each patient, but experience from a Bayer-sponsored phase 1 study with

copanlsisib has suggested the benefit of dihydropyridine calcium channel blockers (*i.e.,* amlodipine, felodipine). Topical nitrates and non-dihydropyridine should also be considered. Addition of non-dihydropyridine can be considered because of low significant clinical DDI potential with these drugs based on results with itraconozole data In general, it is advisable for sites to be prepared, so that anti-hypertensive medication is readily available in case of need.

In the event of the occurrence of arterial hypertension ≥150/90 mmHg during infusion of copanlisib at any cycle, antihypertensive treatment is suggested. In the event of the occurrence of grade 3 arterial hypertension (≥160/100 mmHg) during infusion of copanlisib, the infusion should be interrupted and anti-hypertensive treatment as suggested above is administered. Infusion can be resumed when BP has returned to <150/90 mmHg.

Blood pressure measurement on treatment days

Blood pressure will be measured every 5-10 min prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results <150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 min before blood pressure is recorded.

On infusion days, blood pressure will be measured at 0 hour (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), and 1 hour and 2 hours after the end of infusion.

NOTE: A window of ±10 min is allowed for all BP measurements, except for pre-dose (0 hour) measurement.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for Copanlisib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride, NSC 784727)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are

protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 702 patients.* Below is the CAEPR for Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, June 18, 2019[1]

Adverse Events with Possible Relationship to Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CTCAE 5.0 Term) [n= 702]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		***Muscle cramp (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis[3]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythroderma	
		Pruritus	
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be

distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Pneumonitis is a group term that includes interstitial lung disease, dyspnea, dyspnea at rest, and dyspnea exertional.

Adverse events reported on Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Eosinophilia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Left ventricular systolic dysfunction; Myocardial infarction; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Constipation; Dry mouth; Dyspepsia; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Oral dysesthesia; Oral pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Fever; General disorders and administration site conditions - Other (failure to thrive); Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Infusion related reaction; Injury, poisoning and procedural complications - Other (drug eruption)
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; Investigations - Other (electrocardiogram U wave abnormal); Lipase increased; Lymphocyte count decreased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (blood insulin increased)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (psoriatic arthropathy); Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Amnesia; Dizziness; Dysesthesia; Dysgeusia; Headache; Paresthesia; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome
PSYCHIATRIC DISORDERS - Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (renal insufficiency)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea[3]; Hypoxia; Pleural effusion; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pulmonary congestion)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Purpura; Rash acneiform; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hypotension; Thromboembolic event; Vascular disorders - Other (circulatory collapse)

Note: Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Nivolumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 2, 2020[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hypophysitis[3]		
	Hyperthyroidism[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocytes decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders – Other (immune-mediated nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous disorders -Other (bullous pemphigoid)	
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3] Nivolumab being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic

encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

- PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

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Expedited Adverse Event Reporting

7.2.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.2.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.2.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions."

Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

○ "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.
[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:** • All Grade 3, 4, and Grade 5 AEs **Expedited 10 calendar day reports for:** • Grade 2 AEs resulting in hospitalization or prolongation of hospitalization [2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period. Effective Date: May 5, 2011

7.2.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	CTCAE Grade at which the event will not require expedited reporting[1]
Investigations	Neutrophil count decreased	≤ Grade 2
	Platelet count decreased	≤ Grade 2
	White blood count	≤ Grade 2
	Lymphocyte count decreased	≤ Grade 4
Blood and lymphatic system disorders	Anemia	≤ Grade 2

[1]. These exceptions only apply if the adverse event does not result in ≥24 hours hospitalization.

If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes, for signs and symptoms of progression of the cancer.

7.3 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.4 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at <u>http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm</u>) for more details on how to report pregnancy and its outcome to CTEP.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an

NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 CTEP IND Copanlisib (NSC 784727)

Chemical Name or Amino Acid Sequence: 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride

Other Names: BAY 80-6946 (free base); BAY 84-1236 (dihydrochloride salt)

Classification: Pan class I PI3K inhibitor

Molecular Formula: C23H28N8O4 2HCl

M.W.: 553.45 g/mol

Approximate Solubility: Freely soluble in water and 0.1 M hydrochloric acid (HCl)

Mode of Action: Copanlisib is a pan class I PI3K inhibitor with potent activity against the delta and alpha isoforms. Class I PI3K is downstream of most cancer associated tyrosine kinase growth factor receptors or mesenchymal epithelial transition factor. PI3K delta has a critical role in regulating downstream events of the B-cell receptor.

Description: The powder is white to yellow solid substance.

How Supplied: Copanlisib is supplied by Bayer HealthCare AG and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI. The agent is available as a lyophilized product containing 60 mg of copanlisib in a 6 mL injection vial. The excipients are mannitol, sodium hydroxide, citric acid, and water for injection.

Preparation: Using appropriate aseptic technique, reconstitute the 60 mg vial of copanlisib with 4.4 mL of 0.9% sodium chloride resulting in a concentration of 15 mg/ml. Gently shake well for 30 seconds and allow the vial to stand for 1 minute to let bubbles rise to the surface. Repeat if undissolved substance is still present. The reconstituted solution may be slightly yellow and should be clear prior to being withdrawn from the vial. Withdraw the appropriate volume of the reconstituted solution and further dilute by adding to a 50-200 mL 0.9% sodium chloride bag. Mix well by inverting.

Storage: Store intact vials between 2°C and 8°C.

If a storage temperature excursion is identified, promptly return copanlisib to between 2°C and 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies of the vials are ongoing. The diluted solution should be used immediately (stored up to 4 hours at room temperature including preparation and administration). If the diluted solution for infusion is not used immediately, it is stable for up to 24 hours refrigerated between 2°C and 8°C. It takes approximately 60 minutes for the 100 mL diluted solution to return to room temperature after refrigeration. The infusion should be completed within 24 hours of preparation.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 6 hours after initial entry.

Route of Administration: IV infusion

Method of Administration: The diluted solution for infusion is administered IV over 1 hour. After administration, flush the line to ensure complete dose is given. No IV glucose preparations should be administered on the days of infusion.

Potential Drug Interactions:
In vitro, copanlisib is metabolized primarily via CYP 3A4 and to a minor extent by CYP1A1. It is also a substrate of P-gp and BCRP, but not a substrate of MATEs, OCTs, OATs, or OATPs. Concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Use caution when administered with strong inhibitors and inducers of CYP1A1, P-gp, and BCRP. Smoking tobacco may reduce drug exposure since

tobacco induces CYP1A1 activity.

In vitro, copanlisib is a strong inhibitor of MATE2K. Copanlisib and its metabolite M-1 have a low risk for inhibition or induction of CYP isoforms, inhibition of UGT isoforms, and inhibition of dihydropyrimidine dehydrogenase. Copanlisib does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, bile salt export pump (BSEP), MRP2, or MATE1 at therapeutic 60 mg dose plasma concentrations. Use caution when administered with sensitive drug substrates of MATE2K.

Copanlisib is not an inducer of CYP1A2, 2B6, and 3A.

Copanlisib and its metabolite M-1 have low protein binding.

Special Handling: Copanlisib is not genotoxic in vitro or in vivo. Copanlisib is expected to adversely affect male and female reproduction.

Patient Care Implications:. Females of child-bearing potential and male patients must use adequate contraception while receiving copanlisib and for 1 month after last dose of copanlisib. Do not breastfeed during treatment with copanlisib and for at least 1 month after the last dose of copanlisib.

Hypertension is frequently observed within the first 3 hours after start of infusion and hyperglycemia is frequently observed persisting for approximately 1-3 days after study drug administration. Refer to protocol document for treatment and monitoring guidelines.

Availability

CTEP IND Copanlisib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

CTEP IND Copanlisib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 CTEP and/or CIP IND Nivolumab (NSC 748726)

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: BMS-936558, MDX1106

Classification: Anti-PD-1MAb

M.W.: 146,221 Daltons

Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of

differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to a final concentration of 1-10mg/mls. 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 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Storage: Vials of Nivolumab injection must be stored at 2°- 8°C (36°- 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

S**tability:** Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum

8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Route of Administration: Intravenous infusion over 30 minutes. Nivolumab can be safely infused over 30 minutes in subjects with cancer. Do not administer as an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

Potential Drug Interactions: The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Patient Care Implications: Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

Availability

CTEP IND Nivolumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

CTEP IND Nivolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.3 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.1 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status a "current" password, and active person registration status Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Plan

List of Biomarker Assays in Order of Priority

Prioritization list: Category 1 correlatives (i.e., first to be done): Cell of origin; PD-1/PD-L1/IHC and gene amplification/copy number; Intra-tumoral immune cell locations and number. Category 2 correlative (next in line): PTEN loss and phospho-AKT. Category 3 correlatives: Changes in T-cell profile; cytokine profile; gamma interferon gene signature. Category 4 correlative: cfDNA, mutational burden

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	Cell of origin	Lymph3Cx/ Gene expression profiling	Integrated help determine whether COO predicts response to therapy	M	Baseline /at time of screening	Tissue biopsy (new or archived) FFPE	see section 9.2.1.2	Molecular Diagnostics – Arizona Laboratory, Mayo Clinic Arizona
2	PD1/PD-L1	Immunohistochemistry	Exploratory To be studied as a predictor of response	M	Baseline /at time of screening and any additional subsequent optional biopsies	Tissue biopsy (new or archived)	1x 5-µm paraffin-embedded sections	Stephen Ansell Laboratory, Mayo clinic (Ansell.stephen@mayo.edu)
3	PD1/PD-L1	Gene amplification/copy number by FISH	Exploratory To be studied as a predictor of response	M	Baseline /at time of screening and	Tissue biopsy (new or archived)	1 x 5-µm paraffin-embedded sections	Stephen Ansell Laboratory, Mayo clinic

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
					any additional subsequent optional biopsies			
4	Intratumoral Immune cell location and number	Immunohistochemistry	Exploratory To assess the effects of copanlisib/nivolumab on the immune system within the tumor and tumor microenvironment	M	Baseline/at time of screening and any additional subsequent optional biopsies (if possible D8, at time of progression of disease)	Tissue biopsy	1x 5-µm paraffin-embedded sections	Stephen Ansell Laboratory, Mayo clinic
5	PTEN Loss	Immunohistochemistry	Exploratory To assess for predictors of	M	Baseline/at time of screenin	Tissue biopsy	1x 5-µm paraffin-embedded sections	Stephen Ansell Laboratory, Mayo clinic

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
			response or non-response to therapy		g			
6	Phospho AKT	Immunohistochemistry	Exploratory To assess target inhibition by copanlisib	O	Baseline /at time of screening and any additional subsequent optional biopsies (if possible D8, at time of progression of disease)	Tissue biopsy	1x 5-µm paraffin-embedded sections	Stephen Ansell Laboratory, Mayo clinic
7	Changes in T-cell exhaustion or activation profile	Flow cytometry	Exploratory To define changes in peripheral blood cell populations after treatment	M	At baseline, day 8, day 15, cycle 4 and at time of progress	Whole Blood	1x 10 ml purple top tubes (EDTA)	Stephen Ansell Laboratory, Mayo clinic

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
					ion			
8	Serum Cytokine Profile	ELISA	Exploratory	M	At baseline, day 8, day 15, cycle 4 and at time of progression	Serum	1x 10 ml Red top tube	Stephen Ansell Laboratory, Mayo clinic
9	Mutational burden determination	Whole exome sequencing	Exploratory To assess predictors of response to therapy	O	Baseline /at time of screening	Tissue	1 x -5-µm paraffin-embedded sections	Stephen Ansell Laboratory, Mayo clinic
10	cfDNA	Digital droplet PCR and Next generation sequencing	Exploratory To correlate response to therapy with cfDNA	M	Baseline, day8, day 15 of cycle 1 then cycle 3 and then at time of progression	Whole blood	one cfDNA Streck tubes, 10 ml	Stephen Ansell Laboratory, Mayo clinic

Specimen Collection Schedule

Please provide the type of specimen and the timepoint (study cycle/day) of each specimen collection procedure, and mark the appropriate boxes with an "X" to denote collection on that study day.

Correlative Study	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Cycle 1-Day 8	Cycles 1-Day 15	Cycle 3	Cycle 4	At time of PMD or PD
Tumor biopsy [1]	Mandatory	Tumor	FFPE	see above table for quantity	X[1]	X[2]				X[2]
Peripheral blood	Mandatory	Whole Blood	EDTA (purple top)	10 mL (1 tube)	X	X	X		X	X
Peripheral blood	Mandatory	Serum	Red top tube	10 mL (1 tube)	X	X	X		X	X
Peripheral blood	Mandatory	Whole blood	Streck Cell-Free DNA tubes	10 mL (1 tubes)	X	X	X	X		X

[1] Only obtained when a clinical biopsy is needed. Archival tissue maybe used. If no archival tissue is available, a biopsy then is needed.
[2] Optional additional biopsies at Day 8 Cycle 1 and at time of progression

9.2 Integrated Correlative Studies

9.2.1 Lymph3Cx Cell-of-Origin (COO) molecular subtyping assay – Integrated Laboratory Correlative Study #1 (See Appendix G for more details).

The "Lymph3Cx" assay provides molecular Cell-of-Origin (COO) subtyping of large B cell lymphomas into Germinal Center B cell (GCB), Activated B Cell (ABC), Unclassifiable (UNC), and Primary Mediastinal B Cell Lymphoma (PMBCL) types, which have different biological features such as genomic alterations, gene expression and mutation profiles, signal pathway activation, and prognosis. We hypothesize that, as an integrated biomarker, the Lymph3Cx assay will identify those patients in this trial who benefited from the addition of Copanlisib in combination with Nivolumab.

PMBCL is recognized as a distinct lymphoma entity in the current World Health Organization classification. However, the diagnosis relies on integration of clinical characteristics at time of presentation since reliable distinction from DLBCL solely based on morphological or immunophenotypic features can be difficult and non-reproducible. Gene expression profiling (GEP) studies provide evidence that PMBCL can be distinguished from DLBCL on a molecular level and support a strong relationship between PMBCL and classical Hodgkin lymphoma (Rosenwald et al., J Exp Med 2003; Savage et al., Blood 2003). Because these studies were performed using snap-frozen tissue specimens, the molecular classification of PMBCL has not penetrated into clinical practice. The Lymphoma and Leukemia Molecular Profiling Project research consortium (LLMPP), of which Dr. Rimsza (Rimsza.Lisa@mayo.edu) is the current Principal Investigator, recently developed a robust and accurate molecular assay for the distinction of PMBCL from DLBCL using GEP techniques applicable to routinely available formalin-fixed, paraffin-embedded tissue (FFPE) biopsies.

The Lymph3Cx assay that will be used in this clinical trial is builds upon the well-established Lymph2Cx assay with the addition of a gene expression "module" that specifically identifies PMBCL in addition to the DLBCL subtypes (ABC, GCB, UNC). The Lymph3Cx assay is run on the same platform as Lymph2Cx, the nCounter system by NanoString. The Lymph2Cx assay is now going through commercial development to become an FDA-cleared test. The Lymph2Cx is the only DLBCL cell-of-origin assay at such an advanced stage of development, indicating the quality of the assays by the LLMPP.
For Lymph3Cx assay development, all cases used were centrally reviewed by a panel of expert hematopathologists in the LLMPP. Gene selection was performed using data previously generated on Affymetrix U133 plus 2.0 microarrays and the NanoString platform. The training cohort for the new Lymph3Cx assay consisted of 68 cases (48 DLBCL and 20 PMBCL), and the independent validation cohort was comprised of 88 PMBCL and 78 DLBCL (42 GCB, 26 ABC, 10 unclassified). Cases were required to have a tumor content of > 60% (after macrodissection) and nucleic acids were extracted from 10 µm FFPE scrolls. Digital gene expression was performed using 200 ng RNA and the NanoString technology (Seattle, WA). Fresh versus 14 day old unstained tissue sections, at ambient temperature, were compared and yielded the same results on 5 samples indicating a 2 week time lag between cutting the samples and initiating testing is acceptable. Reproducibility between 2 different technical staff members, pathologists, and instruments was 100% for 9 samples repeated 2 weeks apart. Precision was assessed by repeating 5 cases on 3 different occasions, with 100% concordance. Dilution studies demonstrated that 100ng was the minimal reliable input for the assay. Potentially interfering

substances, including all reagents used in the assay, were tested and demonstrated no interference. The final Lymph3Cx gene set consisted of 64 probes and included the previously described 20 genes of the Lymph2Cx assay. A classifier score was then modeled to account for error probabilities of the pathological classification and cut-points were defined at the 0.1 and 0.9 probability scores. The model, including coefficients and thresholds was then "locked" and applied to the independent validation cohort. The assay yielded gene expression data of sufficient quality in 157/166 cases (94.6 %). Among the pathologically-defined PMBCL, 85% were also classified as such based on the molecular signature. Ten percent were allocated in the "uncertain" category and 5% of cases showed a molecular signature of DLBCL. Among the pathologically-defined DLBCL cases, 83% were classified as DLBCL by the assay, 14% were "uncertain" and 3% were predicted to be PMBCL based on GEP. The newly developed and validated Lymph3Cx assay clearly distinguishes PMBCL and DLBCL based on gene expression signatures and shows high concordance with the pathological classification of an expert hematopathologist panel.

An important pre-analytical variable is percentage of tumor, which should be a minimum of 60% based on a second dilution study demonstrating that 60% and 50% gave reliable results, but that 40%, 30%, and 20% did not. To be conservative, 60% was chosen to allow for slight variability in tumor content estimates and successive cuts off of the block. To address the tumor percent, an H&E stained section of each case will be assessed by Dr. Rimsza, who will estimate tumor purity. If needed, macro-dissection of the tissue sections will be performed to increase tumor content. Optimal input is 1 x 10 micron thick section for a 50mm2 biopsy. For smaller biopsies, proportionally more sections will be taken. Dr. Rimsza will measure the size of the tumor area and determine the number of needed sections at the same time that she determines the tumor content. A Pathology Quality Assurance form is used to document the tissue input specifics (size/number of needed sections and percent tumor). At this time, only formalin fixed biopsies (not other fixatives) have been assessed. The Pathology reports on the biopsies will be reviewed to determine whether formalin or another fixative was used. The average raw count of the housekeeping genes in the assay is used as a final quality control marker – samples with <20 counts for this metric are reported as "Poor Quality". The materials for this study will be analyzed in the exact same manner as the samples in the clinical laboratory that are tested for medical care. A positive and negative control and up to ten samples can be included in each 12-well cassette. Positive control is an equimolar mixture of oligonucleotides which hybridizes with all probes in the assay. This will be lyophilized, reconstituted into stock solutions, and pooled by the manufacturer. The negative control is a well in the cassette that includes all reagents and probes, but no RNA. Importantly, there is a 100% concordance of 10 cases between 3 different laboratories using the Lymph3Cx assay. For these reasons, we chose the Lymph3Cx assay as the molecular method of choice. We have standardized operating procedures, controls, and a completely locked algorithm. Scoring is not applicable in this assay.
The lab performing this assay will be the Molecular Diagnostics – Arizona Laboratory, Mayo Clinic Arizona, CLIA #03D2113087; Medical Director: Dr. Lisa Rimsza; Performing technologist: Colleen Ramsower, MB(ASCP) and Tameson Yip, MB(ASCP). "MB" indicates these staff members are certified in molecular biology by the American Society of Clinical Pathologists. Testing for the proposed trial will follow the exact same procedures as are used for the samples in the clinical laboratory. Dr. Rimsza has extensive experience with the assay. She is the senior author on both the Lymph2Cx publication and Lymph3Cx abstract (manuscript in

preparation), co-inventor on both assay patents, and the Medical Director of a CAP-CLIA certified laboratory performing the Lymph2Cx assay, which is actively testing Mayo Clinic patients since December 2016. This is the first clinical laboratory in the country to offer the Lymph2Cx COO test for patient care. Dr. Rimsza both directs the laboratory and signs the medical results cases.

9.2.1.1 Collection of Specimen(s)

The specimens will be formalin fixed, paraffin embedded (FFPE) tissue sections from the diagnostic pre-treatment biopsies of the patients, processed under standard clinical protocols at each participating site.

9.2.1.2 Shipping of Specimen(s)

An H&E cut contiguously with the unstained sections is required. Tumor Cellularity must be >= 60% (by area), but we have the ability to macrodissect if it is lower.

If the tumor area (based on area containing 60% or more tumor cellularity) is:

- **Greater than or equal to 15mm^2**: send 3 unstained sections (4-5 microns thick) mounted on positively-charged slides, plus one H&E (cut contiguously with unstained sections)
- **Less than 15mm^2**: send 6 unstained sections (4-5 microns thick) mounted on positively-charged slides, plus one H&E (cut contiguously with unstained sections)

Label the slides with the following information:

Protocol # 10193
LM3CX
Patient Study ID and Initials
Date of sectioning
"H&E" or "USS" (depending on whether it is the H&E or the unstained section) and the section # (i.e. H&E-1, USS-2, USS-3, etc., in the order they were cut. Does not have to start with 1, but should be contiguous.).

Performing Lab: Molecular Diagnostics – Arizona Laboratory (MDAZL), Mayo Clinic Arizona, CLIA #03D2113087. Laboratory Director: Lisa M. Rimsza, M.D.

Lab Contact: Colleen Ramsower
Email: Ramsower.Colleen@Mayo.edu
Lab Phone: 480-301-4934

Alternate Contact: Betty Glinsmann-Gibson
Email: Glinsmann-Gibson.Betty@Mayo.edu
Lab Phone: 480-301-9244

Shipping address:

Attn: Colleen Ramsower
Mayo Clinic Arizona
13400 E. Shea Blvd.
SC CR 01 250 MDAZL
Scottsdale, AZ 85259
480-301-4934

Place the slides into shipping containers, and seal in a plastic bag. Ship the slides **overnight** in a padded envelope, **Monday through Thursday only** (packages cannot be received on weekends).

During the months of April-October, include a cool pack with the shipment (bagged separately from the slide containers). [If we don't have some sort of web registration] Email Colleen Ramsower or Betty Glinsmann-Gibson a copy of the manifest as well as the shipment's Tracking Number prior to sending.

9.2.1.3 Site(s) Performing Correlative Study

Performing lab: Molecular Diagnostics – Arizona Laboratory, Mayo Clinic Arizona; Medical Director: Dr. Lisa Rimsza; Performing technologist: Colleen Ramsower, MB(ASCP)CM., Quality Specialist: Tameson Yip, MB (ASCP)cm

9.3 Exploratory/Ancillary Correlative Studies

Unless otherwise indicated, we will follow the same steps for all correlative studies in terms of collection, handling and shipping as stated below in section 9.3.2 and 9.3.3.

9.3.1 Background and Methodology

We propose to obtain tumor tissue, peripheral blood mononuclear cells and serum for biomarker and correlative studies:

- To characterize the effects of the copanlisib and nivolumab combination regimen on tumor cells, tumor microenvironment and the immune response in relapsed/refractory DLBCL and PMBCL
- To assess predictors of response of the combination in relapsed/refractory DLBCL and PMBCL.

We will use the PD1/PD-L1 expression, gene amplification, number and location of immune cells, genetic mutations in the tumor, peripheral cell subtypes and activation status, as well as cytokine profile to develop an immune signature that is associated with response to PD-1 blockade in combination with copanlisib.

Blood/blood product/Tissue samples will be collected for the following research:
1. Identification of intratumoral immune cells by immunohistochemistry (IHC). To assess whether the location or number of intratumoral immune cells predicts response to therapy, serial

5-µm paraffin-embedded sections will be deparaffinized and endogenous peroxidase quenched by incubation in 50% methanol/H2O2. All sections will be pretreated with 50 mmol/L EDTA and staining will be done automatically on DAKO Autostainer using antibodies to CD11c (Leica Microsystems 5D11), CD14 (Cell Marque EPR 3653), CD163 (DAKO 1F8), CD68 (DAKO PG-M1), CXCL13 (R&D Systems 53610), FOXP3 (Abcam 236AE/7), CD3 (R&D Systems), PD-L1 (405.9A11), PD-L2 (366C.9E5) and PD-1 (Abcam NAT). Sections will be viewed with an Olympus BXFA51 microscope and photos taken with an Olympus DP71 camera.

2. Determine whether genetic amplification or copy number gain resulting in PD-L1/2 is associated with response to therapy in our patients. FISH will be performed to assess copy number on chromosome 9p24.1. The bacterial artificial chromosome probes (CHORI; www.chori.org) RP11-599H2O, which maps to 9p24.1 and includes PD-L1 (labeled with Spectrum Orange), and RP11-635N21, which also maps to 9p24.1 and includes PD-L2 (labeled with Spectrum Green), will be cohybridized. A control centromeric probe, Spectrum Aqua–labeled CEP9 (Abbott Molecular) that maps to 9p11-q11, will be hybridized according to the manufacturer's recommendations. Nuclei with a target:control probe ratio of at least 3:1 will be classified as amplified, those with a probe ratio of more than 1:1 but less than 3:1 will be classified as relative copy gain, and those with a probe ratio of 1:1 but with more than two copies of each probe will be classified as polysomic for chromosome 9p.

3. Serum cytokine profile. To determine whether a serum cytokine profile can be used as a predictive biomarker, serum specimens will be subjected to multiplex ELISA (Invitrogen, Camarillo, CA) to measure 30 serum cytokines in pre-treatment and subsequent blood samples. Luminex-200 system version 1.7 will be used for reading plates and MasterPlex QT1.0 system (MiraiBio) will be used to analyze data. Cytokines will include epidermal growth factor (EGF), eotaxin, basic fibroblast growth factor (FGF-b), granulocyte macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), IFN-α, IFN-ϒ, interleukin 1 receptor antagonist (IL-1RA), IL-1β,IL-2, IL-2R , IL-4, 5, 6, 7, 8, 10,12,13,15,17, Inducible protein-10 (IP10/CXCL10), monocyte chemotactic protein 1(MCP-1), monokine induced by interferon γ, (MIG/CXCL9), MIP-1α (CCL3), MIP1β (CCL4), regulated on activation normal T-cell expressed and secreted (RANTES),TNF-α and vascular endothelial growth factor (VEGF). Internal control serum will be included in all assays to control for interassay variation.

4. Changes in T-cell subsets by flow cytometry. To define changes in peripheral blood cell populations after treatment, peripheral blood mononuclear cells will be stained with fluorochrome-conjugated antibodies to human CD69 (R&D Systems), CD3 (clone HIT3a), CD19 (clone 4G7), PD1 (clone EH12.1), CD14 (clone M5E2), CD163 (clone GH1/61), CD21 (clone B-ly4), PD-L2 (clone M1H18), PD-L1 (clone M1H1), TIM3 (clone 344823), and CD23 (clone EBVCS-5; all obtained from BD Biosciences) and the data will be analyzed using CellQuest software (Becton Dickinson).

5. Sequencing to determine mutational burden. To determine whether increased numbers of mutations correspond to increased responses to therapy, genomic DNA will be extracted from formalin-fixed, paraffin- embedded tissue blocks for mutational analysis. DNA will be extracted using the Qiagen FFPE DNA extraction kit. DNA quantitation will be performed using a Qubit fluorometer prior to sequencing. Whole-exome capture libraries constructed via the Agilent

Sure-Select Human All Exon v2.0, 44Mb baited target with the Broad in-solution hybrid selection process will be used. Enriched exome libraries will be sequenced on the HiSeq 2000 platform (Illumina) to generate paired-end reads (2x76bp) to a goal of 150X mean target coverage (Broad Institute, Cambridge, MA). Targeted resequencing using a custom panel of 376 loci to a target coverage of 500X will be performed using Ampliseq (Life Technologies).

6. Screening for PTEN Loss. The following methods were developed and validated using standard approaches for clinical test validation, in line with CLIA provisions and CAP requirements at MDACC (in collaboration with Dr. Timothy Yap) clinical IHC laboratory, which is certified under the provisions of the United States Clinical Laboratory Improvement Act (CLIA) and accredited by the College of American Pathologists (CAP). This laboratory is also the central laboratory for the PTEN immunohistochemical study for the National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH) trial. The anti-human PTEN antibody clone 6H2.1 (isotype IgG2a, kappa) is manufactured by Dako and registered with the Food and Drug Administration (FDA) for in vitro diagnostic use (IVD). Per Dako, the immunogen against which the antibody is produced is the full-length recombinant human PTEN protein. This is a monoclonal mouse anti-PTEN clone 6H2.1 which identifies a single band at the 55 kD-predicted molecular weight for PTEN in western blots of MCF-7, T-47D and MDA-MB-435S PTEN-homozygous cell lines. PTEN-null cell lines BT-549 and MDA-MB-468 were unreactive with clone 6H2.1 by western blot analysis. Immunoblots of MCF-7 cells induced to express PTEN demonstrated an increased band intensity at the expected size, while a weak band was observed on immunoblots of ZR-75-1 cell lysates containing a hemizygous deletion of PTEN and a missense mutation in the remaining allele. Immunohistochemical staining of sections from FFPE blocks of Ishikawa 3-H-12 cells transfected with PTEN stained positively, whereas PTEN-deficient 3-H-12 cell block sections were unreactive. The anti-PTEN antibody is provided in liquid form as a tissue culture supernatant (containing fetal bovine serum) at a concentration of 222.4 mg/L dialyzed against 0.05 mol/L Tris-HCl, pH 7.2, and 0.015 mol/L sodium azide, and containing stabilizing protein.

This antibody can be used to perform IHC on formalin-fixed paraffin-embedded (FFPE) tissue sections and has been in use since 2010. The final protocol is validated for use on 4 um FFPE tissue sections. In brief, following deparaffinization and rehydration of the tissues sections, antigen retrieval is performed at 100 °C for 20 minutes with Tris-EDTA buffer, pH 6.0. Endogenous peroxidase is blocked with 3% peroxide for 5 minutes. Primary PTEN antibody (Dako, clone 6H2.1) is applied at 1:100 dilution. Primary antibody detection is carried out using a commercial polymer system (Bond Polymer Refine Detection, Leica), and staining development is achieved by incubation with DAB and DAB Enhancer (Leica)

A positive and negative control is added to every IHC run (batch control) and is reviewed by a member of the IHC medical directorship team. Records of batch control results are documented daily in internal laboratory records.

Correlatives (1 to 6) will be done at Stephen Ansell's laboratory (Chair of lymphoma disease oriented group). Dr. Ansell has extensively studied the effects of immunotherapy on the tumor and tumor microenvironment and has published several papers in the topic. These correlatives will be exploratory.

7. Circulating free DNA (cfDNA). Correlate effects of therapy on cfDNA and correlation with degree of response and use as an early predictor of progression of disease. Plasma samples from patients will be screened for cfDNA at the end of the trial. We will develop and optimize digital droplet PCR-based assays on the customizable RainDrop Digital PCR System (http://raindancetech.com/digital-pcr-tech/raindrop-digital-pcr-system). We will use the best technology available at the end of the trial as this is a rapidly evolving area of research.

9.3.2 Handling and shipping of blood specimen(s)

9.3.2.1 Kits

- Kits will be used for this study. Kits will contain supplies and instructions for collection, processing and shipping specimens
- Participating sites may obtain kits by emailing: henderson.kimberly@mayo.edu. Email requests should include address, contact information and number of kits being requested.
- Kits will be sent via FedEx Ground at no additional cost to participating sites. Allow 3-4 business days to receive kits.

9.3.2.2 Packing and Shipping Instructions:

Peripheral blood samples should be shipped the same day they are collected (Monday-Thursday). They should be shipped priority overnight taking care to avoid Friday collection and shipping.

If unavoidable, Friday shipping with Saturday delivery can be arranged contacting the laboratory **in advance**. Please notify Mayo Clinic by email henderson.kimberly@mayo.edu or phone (507) 284-3805 to notify laboratory when specimens are being shipped.

See Appendix I for additional details

Please email Kim Henderson at Henderson.kimberly@mayo.edu or call 507-284-3805 to notify the laboratory when samples are being shipped. Indicate the protocol number MC1787/10193, the Fed Ex tracking number, name and phone number of the contact person. The samples in prepared kits should be shipped to the following:

Mayo Clinic
Attn: Stacey Lehman
Stabile 613
221 4th Avenue SW Stabile
Rochester, MN 55905

9.3.3 Handling and shipping of tissue specimen(s)

9.3.3.1 Collection of Specimen(s): FFPE tumor tissue

9.3.3.2 Handling and Shipping of Specimen(s): FFPE tumor blocks are preferred. Alternatively, unstained glass slides from FFPE are acceptable. Please include a copy of the de-identified surgical pathology report, as well as study, site and patient study numbers. All FFPE specimens for correlative studies may be shipped together.

Shipping Procedure:

1. Place the block or slides in small zip-lock bag and seal.
2. Insert the bag containing the block or the slides in a bubble wrap bag.
3. Place wrapped samples inside the largest compartment of specimen biohazard bag and seal.
4. Insert a copy of the de-identified surgical pathology report in the outer pocket of the specimen biohazard bag.
5. Include a refrigerated cold pack (not frozen) if shipping in the summer months.
6. Place the specimen biohazard bag into the box and close.
7. Complete the transport documents and place into waybill pouch; affix to box.
8. Ship package to Mayo Clinic at the address below.
9. Please send email on the day of the shipment.

Please send FFPE tissue to:
Mayo Clinic
Attn: Stacey Lehman
Mayo Clinic
Stabile 613
221 4th Avenue SW
Rochester, MN 55905

10. STUDY CALENDAR

Baseline laboratory evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done < 4 weeks prior to the start of therapy. Pre-study labs must be done ≤7 days prior to start of therapy. Windows of ± 1 to 2 days are permissible for cycles 1, 2 and 3; windows of ± 3 days are permissible for cycles 4 and beyond. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1			Cycle 2			Cycle 3-8			Cycle 9 and beyond			Off Study[e]
		D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	
Copanlisib		C	C	C	C	C	C	C	C	C	C		C	
Nivolumab		N		N	N		N	N		N	N			
Informed consent	X													
Physical exam[1]	X	X	X	X	X	X	X	X			X			X
Oxygen saturation	X	X	X	X	X	X	X	X	X	X	X		X	X
Lab tests [a]	X	X	X	X	X	X	X	X	X	X	X		X	X
B-HCG	X[b]													
Evaluation of Cardiac Function[f]	X													
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X		X	X
Radiologic evaluation	X	Radiologic measurements should be performed every 12 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease												
FFPE for correlatives	X[c]		X[c]											X[c]
Blood for correlatives[d]	X		X	X				X						X

C: Copanlisib: Dose to be determined after a safety run-in given IV on days 1, 8 and 15 during every 28-day cycle for cycles 1-8. Cycle 9 and beyond, IV will be given on days 1 and 15.

N: Nivolumab: ***All patients:*** 240 mg given IV on days 1 and 15 for cycles 1 through 8 followed by 480 mg on day 1 only of all subsequent cycles thereafter

1. Physical exam includes demographics, medical history, concurrent medications, vital signs, performance status, weight and at pre-study only, height.

a: Lab tests to be performed at baseline and within 72 hours prior to each study drug

administration include CBC with differential and chemistry: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN/urea, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Laboratory test monitoring will continue as long as patient continues to receive study treatment.

b: Serum or urine pregnancy test for females of childbearing potential. A serum or urine pregnancy test is required within 24 hrs of starting study treatment

c. Archived tumor tissue should be submitted at pre-study. If no tissue is available, a new biopsy must be performed. Additional optional tumor tissue biopsies can be performed at Day 8, Cycle 1 and at time of disease progression.

d: Blood draws for research are performed at pre-study, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 4 Day 1 and at disease progression. cfDNA will be done at baseline, Cycle 1 Day 8, Cycle 1 D15, Cycle 3 Day 1 and at time of disease progression. Blood should be drawn prior to treatment.

e: Off-study evaluation to be performed 30 days after the last dose of study drug. Patients are followed for at least 100 days for AE assessment.

f: Perform an evaluation of cardiac function including ECG and echocardiogram and Troponin for all patients at screening, and thereafter as clinically indicated. Also perform an evaluation for patients with evidence of CHF, MI, cardiomyopathy, or myositis including lab tests and cardiology consultations including ECG, echocardiogram, CPK and troponin as clinically indicated

11. MEASUREMENT OF EFFECT

If a second confirmatory scan indicates unequivocal disease progression, the subject will be discontinued from treatment. The date of the first scan indicating progression will be used for analysis purposes. If however the second scan indicates a reduction in tumor burden or stable disease from the baseline scan, the subject may continue on treatment in the absence of unacceptable toxicity or other reason for treatment discontinuation.
Notwithstanding, the Investigator is free to remove the patient from treatment at any time during the study if it is felt to be in the patient's best interest.

11.1 Antitumor Effect – Hematologic Tumors

Lugano Classification Response Criteria

11.1.1 Response Considerations

Definitions for clinical response for patients with lymphoma are based on the lymphoma response to immunomodulatory therapy criteria or LYRIC.(Cheson et al. 2016) Lymph node measurements should be taken from the CT portion of the PET/CT, or other dedicated CT scans where applicable. Measurement of lymphadenopathy for purposes of assessing for PR will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). The perpendicular diameter of a single node is sufficient to evaluate for PD (see Table 11.1.2). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically and pathologically negative.

For response assessment, PET-CT is preferred for staging of FDG-avid lymphomas and CT scan is preferred in the other lymphomas

Progressive disease is based on either PET-CT based (PMD) or CT based (PD) response criteria. Definition of progressive disease according to LYRIC is same as the Lugano classification except that a new category of indeterminate response (IR) is added. Patients whose disease fall in the IR category may continue treatment for additional 12 weeks if the patient remains clinically stable as judged by the treating physician. A repeat imaging study in 12 weeks (or earlier if clinically indicated) is mandatory to confirm or refute disease progression. PET confirmation of progressive disease is per physician discretion.

11.1.2 Lymphoma Response to Immunomodulatory Therapy Criteria [LYRIC] (adapted from Cheson et al., 2016)

	PET-CT Based Response	CT-Based Response
Complete Response (CR)	**Complete metabolic response (CMR)**	**Complete radiologic response (CR) (all of the following)**
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (*e.g.,* with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extra lymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response (PR)	**Partial metabolic response (PMR)**	**Partial remission (PR) (all of the following)**
Lymph nodes and extra lymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal

	PET-CT Based Response	CT-Based Response
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not Applicable
No Response or Stable Disease	**No metabolic response (NMR)**	**Stable disease (SD)**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not Applicable
Indeterminate Response (IR)		
IR(1)[b]		≥ 50% increase in SPD of up to 6 measurable lesions in first 12 weeks without clinical deterioration. **Note:** The measurements from the first IR (1) time point becomes the reference against which future assessment will be compared. An increase of ≥ 10% (in addition to an increase of ≥ 5 mm in either dimension of ≥ 1 lesion for lesions ≤ 2cm and 10 mm for lesions > 2 cm) constitutes PD
IR(2)		< 50% increase in SPD of up to 6 measurable lesions with: a. new lesion(s), or b. ≥ 50% increase in PPD of a lesion or set of lesions at any time during

	PET-CT Based Response	CT-Based Response
		treatment. **Note:** The new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. In future assessments, if the SPD of the newly defined set of target lesions has increased ≥ 50% from their nadir value (which may precede the IR time point), the patient should be considered to have PD.
IR(3)	Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number. **Note:** Because inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted below.	
Progressive disease (PD)	***** Excludes patients who meet criteria for Indeterminate Response (IR) *****	
	Progressive metabolic disease (PMD)	**Progressive disease (PD) requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (*e.g.*, a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Extranodal lesions		
Non-measured	None	New or clear progression of

	PET-CT Based Response	CT-Based Response
lesions		preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (*e.g.*, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

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

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

b. If a patient is assessed as having IR and then "true" PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR. We recognize that these lesions may remain stable during the time of observation, but, even if this is the case,

	PET-CT Based Response	CT-Based Response
the initial designation of IR should be changed to PD.		

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Study Oversight

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

NA

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

NA

12.6 Incidental/Secondary Findings Disclosure Procedure

NA

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints:

13.1.1 Overview

This is a parallel phase II study of Nivolumab and Copanlisib in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL). It is designed using two separate a one-stage designs with an interim analyses based on the Simon optimal design to assess efficacy (ORR (CR+PR)).

13.1.2 Primary Endpoint

The primary endpoint is the proportion of objective responses (either a CR or PR according to Lugano criteria). Throughout Section 13.0, CR or PR will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

DLBCL and PMBCL will be analyzed and reported separately.

13.1.3 Statistical Design

13.1.3.1 Decision Rules are based upon prior response rates reported in sections 2.2.1 and 2.2.2.

It is expected that this dose will have response rates similar to those presented.

13.1.3.2 Safety Cohort

This treatment regimen has been explored in previous studies but study results have not been reported, thus, it has been determined that a safety cohort is necessary to confirm the copanlisib dose.

6 patients will be enrolled on the trial and accrual will cease until these six patients have been evaluated for adverse events in 1 cycle. If 1 or 0 of 6 patients experience a DLT as defined in section5.1.3.3 , the study will open enrollment to accrue the rest of the patients. If 2 or more of 6 patients experience a DLT, the trial will be halted while the examination of the treatment regimen at a lower dose will be explored. If it is determined that a lower dose is appropriate, 6 patients will be accrued at the lower dose and accrual will cease until these six patients have been evaluated for adverse events in 1 cycle. If 1 or 0 of 6 patients experience a DLT as defined in section5.1.3.3 , the study will open enrollment to accrue the rest of the patients. If no DLTs are observed at dose level 1, the study will open to complete accrual. If 1 or less patients experience DLTs at dose level -1, the study will open to complete accrual. If 1 or less patients experience DLTs at dose level 1, the study will open to complete accrual.

This decision rule is based on the decision rules for a standard cohorts of 3 trial design. The safety cohort will not be separated by lymphoma subtypes as it is expected that the treatment regimen will have the same effect on all three lymphoma subtypes. The 6 patients accrued at the acceptable dose will be included in the primary analysis.

13.1.3.3 DLBCL: The largest success proportion where the proposed treatment regimen would be considered ineffective in DLBCL is 25%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 45%. This design uses 44 evaluable patients to test the null hypothesis that the true complete response rate is at most 25%.

13.1.3.3.1 Interim Analysis: Enter 14 evaluable patients into the study. If there are three or less successes observed in the first 14 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 4, we will continue accrual.

13.1.3.3.2 Final Decision Rule: If 14 or fewer successes are observed in the first 44 evaluable patients, we will consider this regimen ineffective in this patient population. If 15 or more successes are observed in the first 44 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

13.1.3..3.3 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.3.4.

13.1.3.3.4 NOTE: We will not suspend accrual at the interim analysis to allow the first 14 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety and efficacy data on these patients before re-opening accrual to further patients.

13.1.3.4 PMBCL: The largest success proportion where the proposed treatment regimen would be considered ineffective in PMBCL is 30%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 50%. This design uses 46 evaluable patients to test the null hypothesis that the true complete response rate is at most 30%.

13.1.3.4.1 Interim Analysis: Enter 22 evaluable patients into the study. If there are 7 or less successes observed in the first 22 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 8, we will continue accrual.

13.1.3.4.2 Final Decision Rule: If 17 or fewer successes are observed in the first 46 evaluable patients, we will consider this regimen ineffective in this patient population. If 18 or more successes are observed in the first 46 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

13.1.3.4.3 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.3.4.

13.1.3.4.4 NOTE: We will not suspend accrual at the interim analysis to allow the first 22 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety and efficacy data on these patients before re-opening accrual to further patients.

13.2 Sample Size/Accrual Rate

13.2.1 This study is expected to require a minimum of 42 (6 safety cohort, 14 DLBCL and 22 PMBCL) and a maximum of 96 (6 safety cohort, 44 DLBCL and 46 PMBCL) evaluable patients. We anticipate accruing 10 (10%) additional patients to account for ineligibility, cancellation, or other reasons. Therefore, the study is expected to accrue a maximum of 106 patients overall.

13.2.2 Accrual Rate and Study Duration: The anticipated accrual rate for the safety cohort is 2-3 months. The anticipated accrual rate is 3-5 patients per month for the DLBCL cohort and 1-2 patients per month for the PMBCL group. Therefore, after assessing safety, the accrual period is expected to be 11 months for the DLBCL cohort, with the primary endpoint evaluated at approximately 17 months after the trial opens (or after the last patient accrued has been observed for at least 6 months and data collection for the induction phase is complete). The accrual period is expected to be 31 months for the PMBCL cohort, with the primary endpoint evaluated at approximately 37 months after the trial opens. The total study duration is expected to maximally be 6.75 years, or until all patients have completed all cycles of treatment.

13.2.3 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions and the probability of stopping accrual after the interim analysis can be tabulated as a function of the true success proportion.

For DLBCL:

If the true success proportion is...	0.25	0.30	0.35	0.40	0.45
Then the probability of declaring that the regimen warrants further study is…	0.097	0.286	0.543	0.766	0.901
and the probability of stopping after the interim analysis is …	0.521	0.355	0.221	0.124	0.063

For PMBCL:

If the true success proportion is...	0.30	0.35	0.40	0.45	0.50
Then the probability of declaring that the regimen warrants further study is…	0.097	0.279	0.532	0.762	0.905
and the probability of stopping after the interim analysis is …	0.671	0.474	0.290	0.152	0.067

13.2.4 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

13.3 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by race, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial, the sample size is not increased in order to provide additional power for subset analyses.

The diagnosis is more common in men, as the male:female ratio is approximately 2:1 (Weisenburger et al. 2011)

Based on prior ACCRU studies involving similar disease sites, we expect the racial distribution by gender subsets as shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	**1**
Asian	2	3	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	1	0	0	**1**
Black or African American	5	8	0	0	**13**
White	28	50	1	3	**82**
More Than One Race	1	2	0	0	**3**
Total	**36**	**65**	**1**	**3**	**106**

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13.4 Grouping Factors

13.4.1 Histology: DLBCL vs PMBCL

13.5 Evaluation of Response

13.5.1 Primary Outcome Analyses:

13.5.1.1 The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (Duffy D 1987).

13.5.2 Secondary Outcome Analyses: These analyses will include all patients meeting the eligibility criteria who have signed a consent form and have begun treatment, including patients who fail to achieve a complete or partial response.

13.5.2.1 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

13.5.2.2 Progression free survival time is defined for all evaluable patients as the time from registration to relapse or death due to any cause. Patients are censored if they have not achieved progression at the time of analysis. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier. In addition, the progression-free survival rate at 5 years after registration will be reported.

13.5.2.3 Duration of response is defined for all evaluable patients who have achieved a CR or PR as the date at which the patient's objective status is first noted to be a CR or PR to the earliest date relapse is documented. The distribution of duration of complete response will be estimated using the method of Kaplan-Meier.

13.5.2.4 Overall survival time is defined as the time from registration to death due to any cause. Patients are censored if they are alive at the time of analysis. The distribution of survival time will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958).

13.5.3 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

13.6 Evaluation of Toxicity:

13.6.1 The study statistician will review the study weekly to monitor accrual, endpoints and adverse events. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

13.6.2 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we

observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 2 or more patients in the first 10 treated patients (20%) experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 10 patients have been treated, 20% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

13.7 Results Reporting on ClinicalTrials.gov:

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 5.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 2 months.

REFERENCES

REFERENCES

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

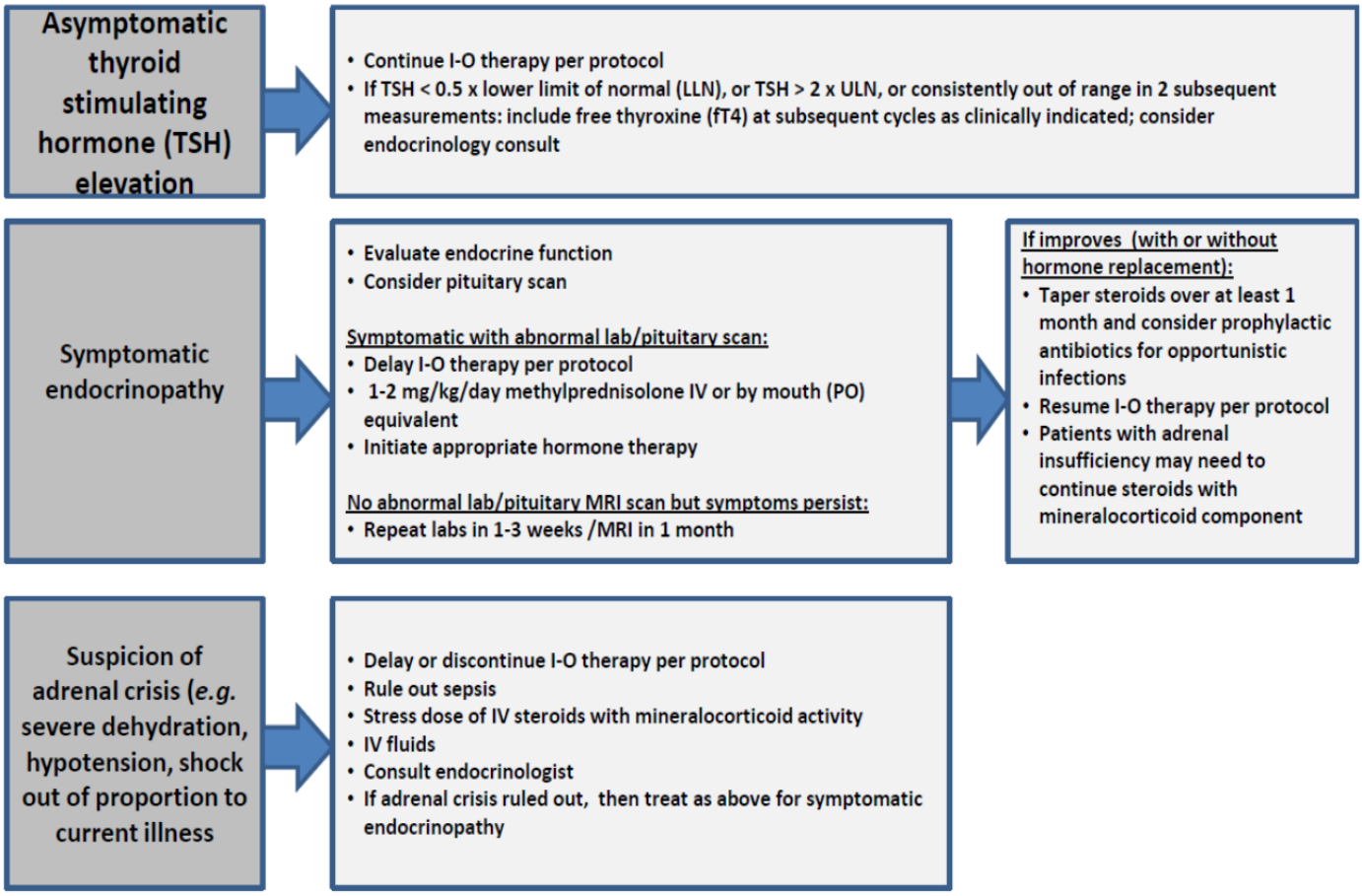
cancer.gov | clinicaltrials.gov

Version *mm/yyyy*

APPENDIX C MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

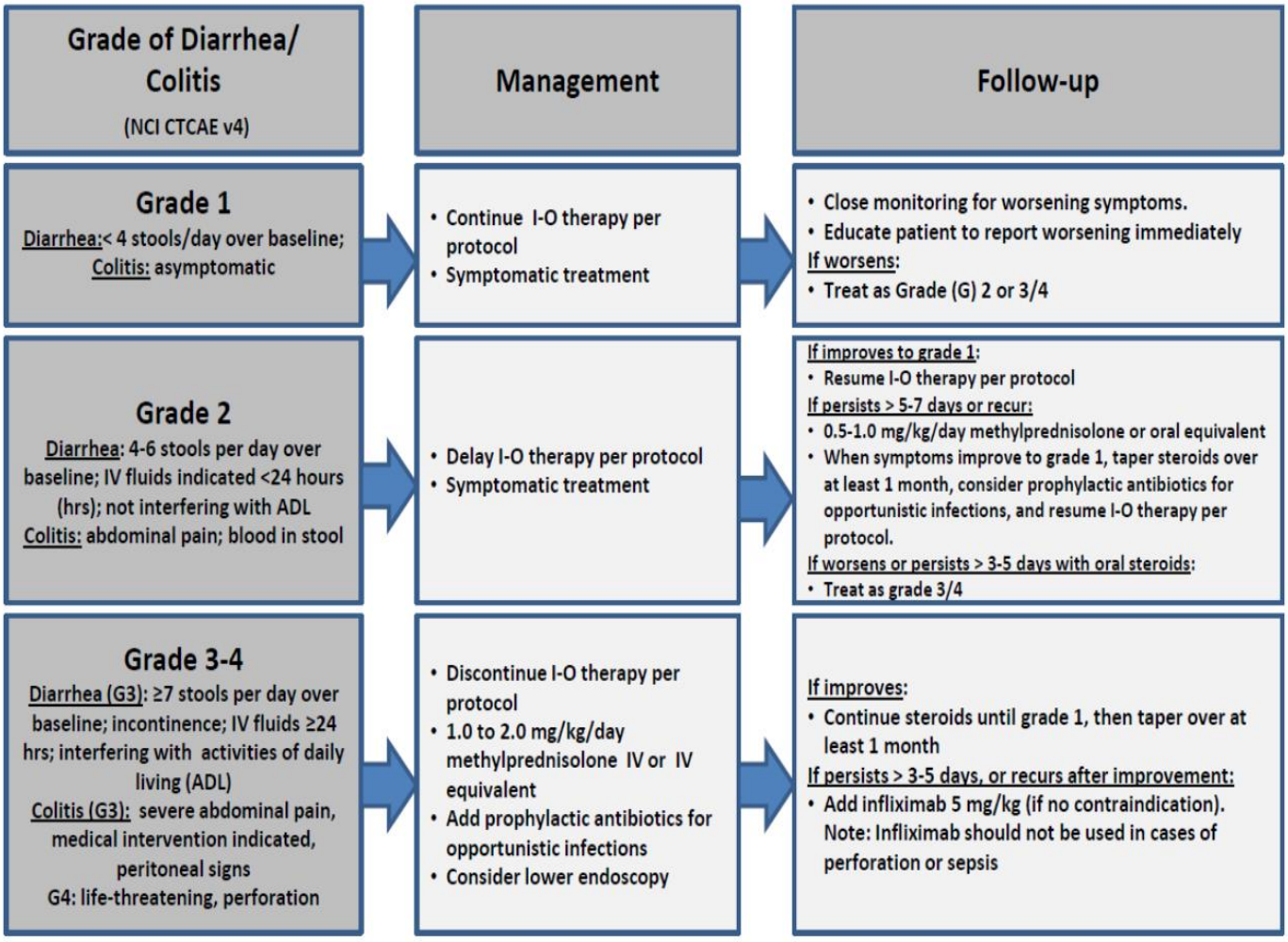
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

GI Adverse Event Management Algorithm

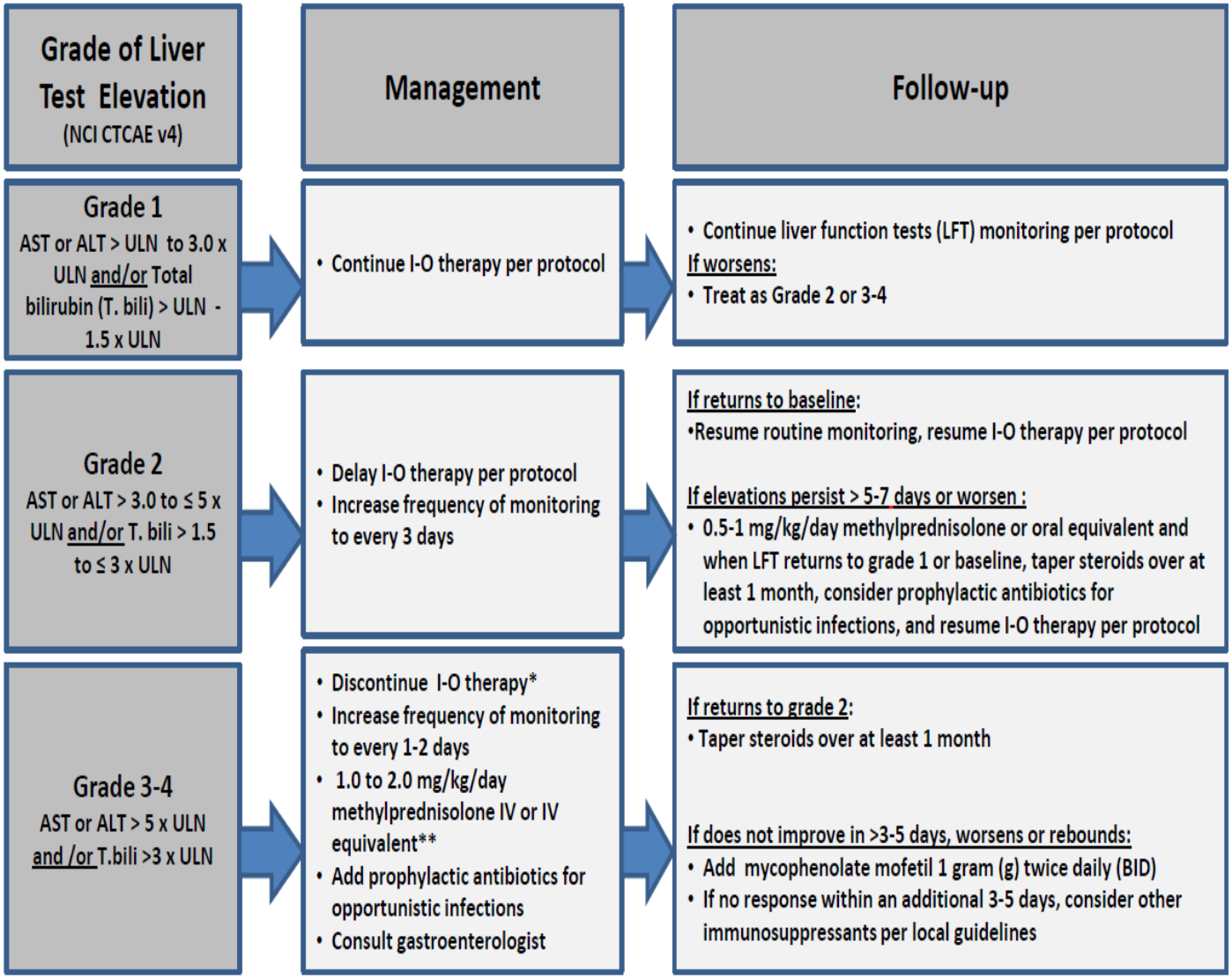
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

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.



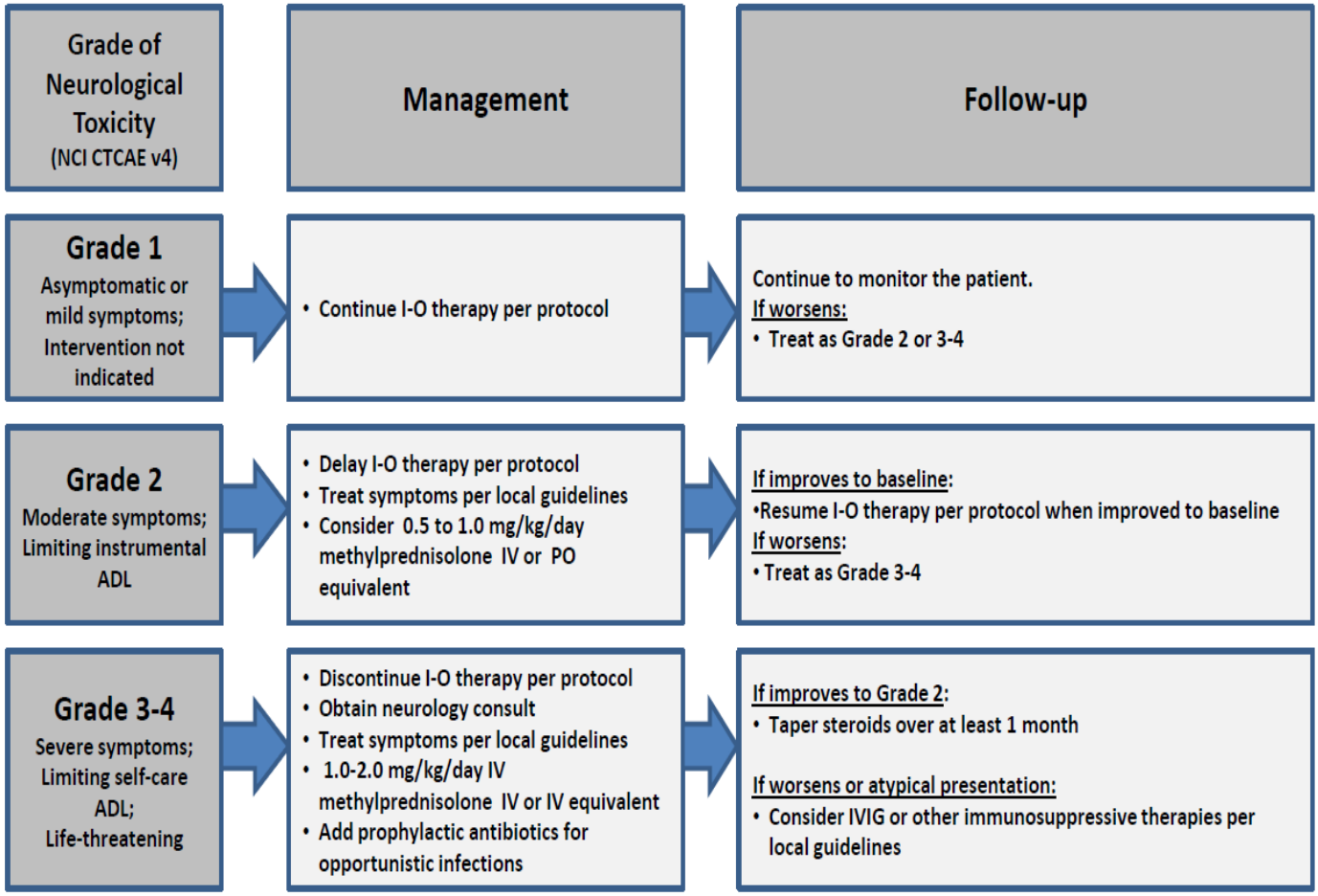
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

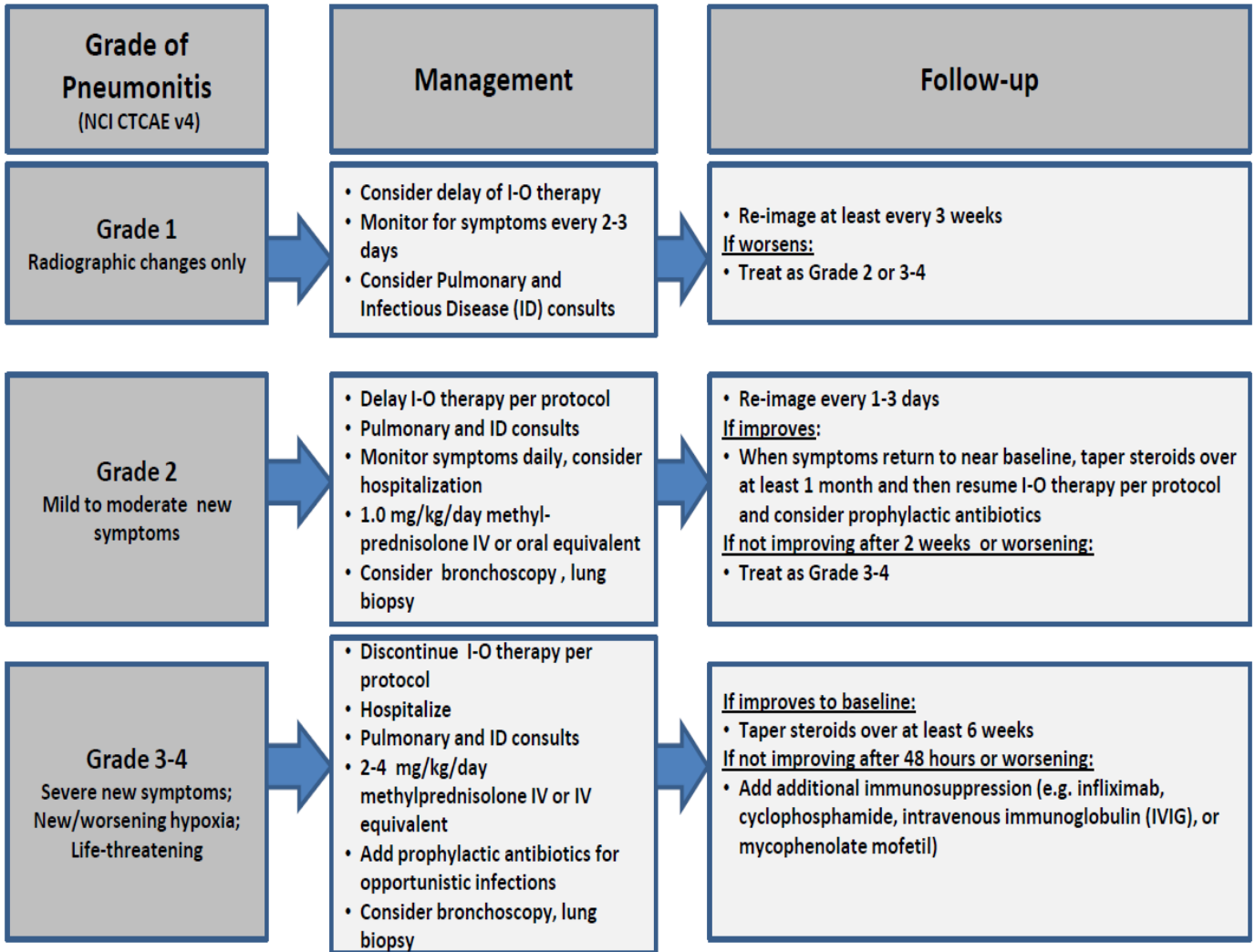
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Pulmonary Adverse Event Management Algorithm

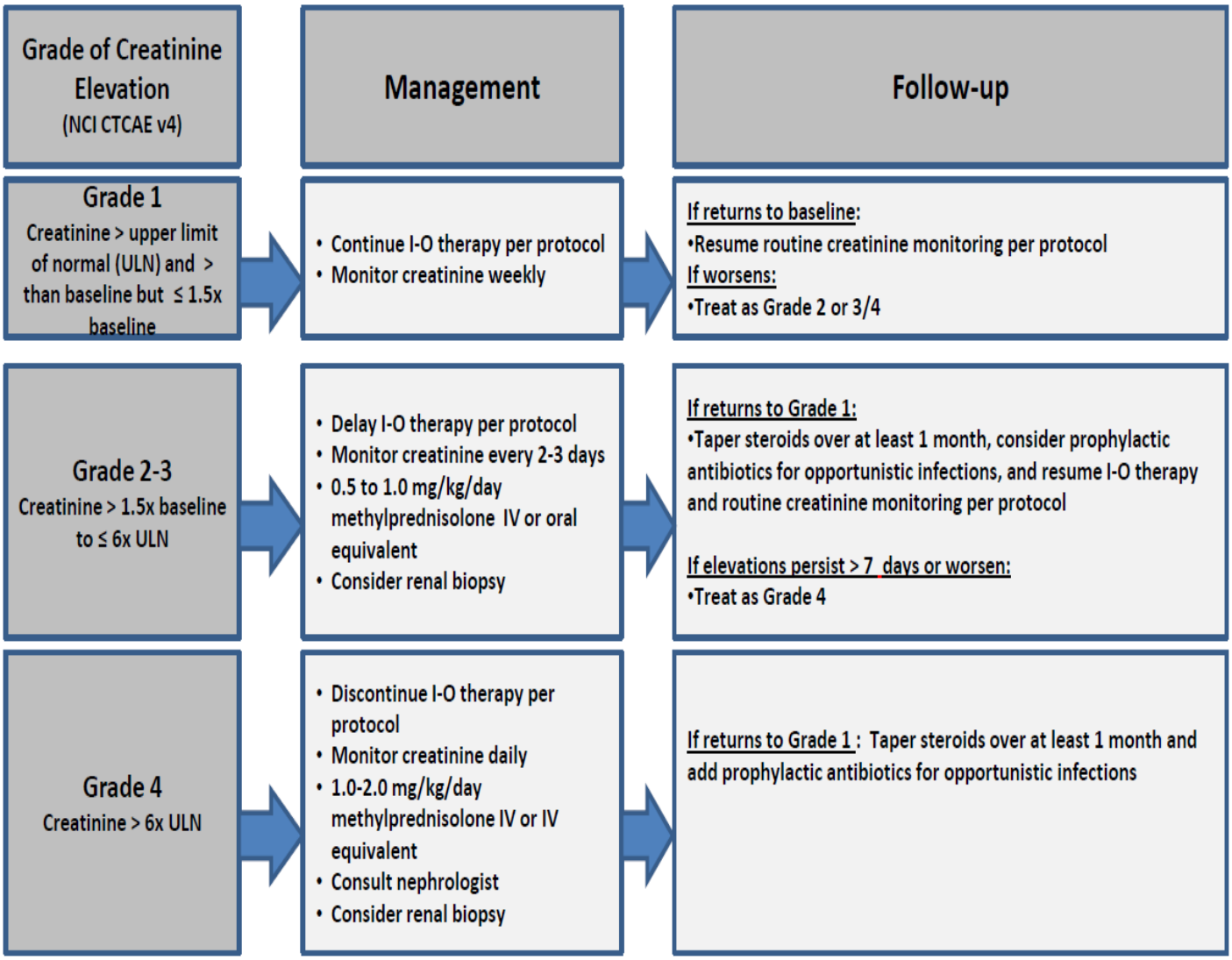
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

Renal Adverse Event Management Algorithm

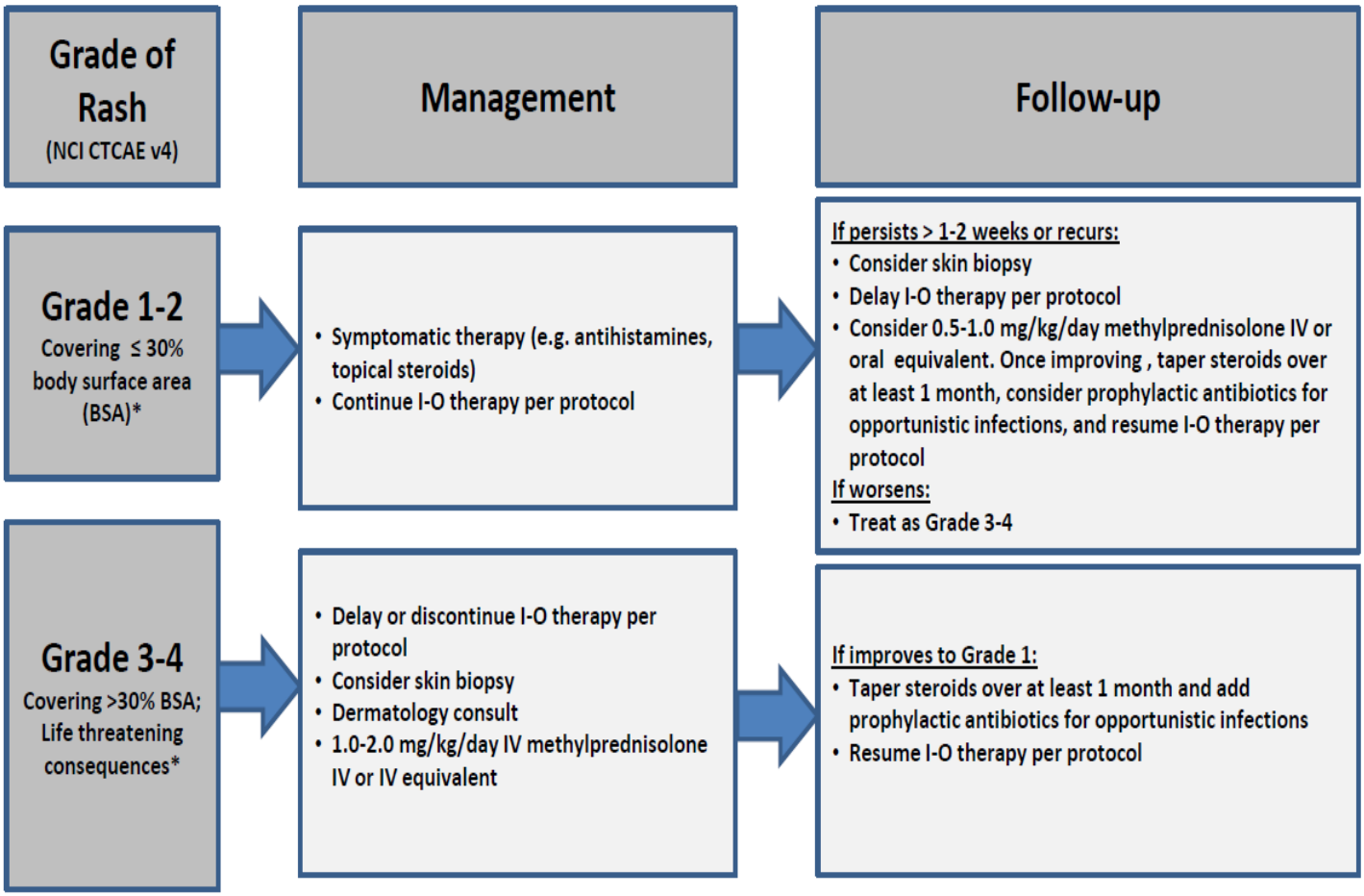
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

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.

APPENDIX D MANAGEMENT OF TRANSIENT GLUCOSE INCREASE ON THE DAY OF COPANLISIB INFUSION

Criteria	Recommendation	Suggested Treatment
Asymptomatic glucose increases ≤250mg/dL	Does not generally require treatment with glucose lowering medication.	**None**
Asymptomatic glucose increase > 250 mg/dl	• Should have repeated laboratory glucose determination. • If the repeated glucose value is decreasing, the glucose may be followed without glucose lowering medication treatment if hydration status is normal as clinically assessed. • Consultation with endocrinologist is recommended	• Hydration if appropriate • **When planning next infusion consider prophylaxis with oral glucose lowering medication**
Symptomatic or persisting glucose increases >250mg/dL	• Hydration status should be clinically assessed. • If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV). • Laboratory test confirming increase should be repeated. If the repeated glucose value is persistent and/or patient is symptomatic and/or the hydration status indicates the need for hydration, glucose lowering medication should be administered. • Prompt input from a diabetes specialist should be obtained.	• Hydration if appropriate • Rapid/ short acting insulin may be given for glucose persisting at >250 mg/dL, or if the patient is symptomatic during the infusion day. • Rapid/short acting insulin • according to the institution sliding scale coverage of glucose persisting at >250 mg/dL is recommended, with oral or IV hydration as clinically appropriate **When planning next infusion consider prophylaxis with oral glucose lowering medication**

APPENDIX E MANAGEMENT OF TRANSIENT GLUCOSE INCREASE ON SUBSEQUENT DAYS FOLLOWING COPANLISIB INFUSION

Criteria	Recommendation	Suggested Treatment
Max post infusion glucose >200 mg/dL noted on subsequent days	• Oral Glucose Lowering Medication Recommended on subsequent days. • **Consultation with endocrinologist is recommended.**	• The use of sulphonylurea/metaglinides, isnulin secretagogues medications to manage increased glucose levels post drug infusions is not recommended. • Treatment with glucose lowering medication suggested according the local standards of practice. • Based on mechanisms of action and decreased risk of hypoglycemia, metformin, SGLT-2-inhibitor or DPP4-inhibitor might be useful treatment options

APPENDIX F DOSE MODIFICATION OF COPANLISIB FOR ARTERIAL HYPERTENSION

Toxicity (CTCAE)	Study drug action	Recommendation
Pre-dose measurements BP ⩾150/90 mmHg	No dose should be given until recovery to <150/90 mmHg.	Consider BP lowering medication. Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to <150/90 mmHg. If BP doesn't return to <150/90 mmHg, delay dosing until next visit.
During infusion: CTCAE hypertension of grade 3 or ⩾160/100 mmHg	Infusion can be interrupted or slowed down and administration of BP lowering therapy should be initiated.	Infusion may be resumed when BP has returned to <150/90 mmHg at the investigator's discretion or skipped. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b]
Post-dose: Drug-related CTCAE hypertension of grade 3 or ⩾160/100 mmHg [a]	–	Administration of BP lowering therapy should be initiated according to local standard of care. Additional measurements to be performed as clinically indicated until recovery to <150/90 mmHg. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b]
CTCAE hypertension of grade 5	Permanent discontinuation	–

CTCAE = Common Terminology Criteria for Adverse Events; BP = Blood pressure
[a]: Not manageable despite optimal antihypertensive treatment.
[b]: The lowest dose level is 45 mg.

APPENDIX G BIOASSAY TEMPLATES

Study Checklist for CTEP-Supported Early Phase Trials with BIOMARKER ASSAYS

INSTRUCTIONS: For INTEGRAL assay, respond to Items 1-7.
For INTEGRATED assay, respond to Items 1-3 and 5-7.
(In lieu of completing items 5-6, the biomarker assay templates available at http://www.cancerdiagnosis.nci.nih.gov/diagnostics/templates.htm **may be utilized.)**

Please submit a response to each of the criteria below and complete one Study Checklist for each Biomarker endpoint.

1. Name of marker: **Lymph3Cx Cell-of-Origin (COO) molecular subtyping assay for Primary Mediastinal B cell Lymphoma (PMBCL) and Diffuse Large B Cell Lymphoma (DLBCL) subtypes**

2. For an integral or integrated assay, indicate the role(s) of the biomarker assay in the trial:

   A. Eligibility criterion
   B. Assignment to treatment
   C. Stratification variable
   D. Risk classifier or score
   E. Other (describe in detail): **This assay provides molecular cell-of-origin (COO) subtyping of PMBCL, not PMBCL, and uncertain; and DLBCL, with DLBCL further divided into Activated B cell, Germinal Center B cell, and Unclassifiable subtypes. These tumor types have different biological features such as gene expression, mutation profiles, signal pathway activation, and prognosis. Retrospectively, after closure of the trial, the Lymph3Cx results will be analyzed with regard to patient response to the novel chemotherapy regimen. The assay was developed by the Lymphoma and Leukemia Molecular Profiling Project research consortium (LLMPP), of which Dr. Rimsza is the current Principal Investigator.**

3. Identify the specific individual(s) and laboratory(ies) who are being considered for conducting the assay(s) for the trial. **Performing lab: Molecular Diagnostics – Arizona Laboratory, Mayo Clinic Arizona; Medical Director: Dr. Lisa Rimsza; Performing technologist: Colleen Ramsower, MB(ASCP)^{CM}., Quality Specialist: Tameson Yip, MB (ASCP)$^{cm.}$**

4. Integral laboratory assays used for clinical decision-making must be performed in a CLIA-certified facility. Provide the lab's CLIA number that is performing the integral biomarker study(ies) and the expiration date of the certificate. N/A – **The Lymph3Cx assay will be an Integrated Assay, not used for medical decision-making; nevertheless, the study will be conducted in the Molecular Diagnostics of Arizona Lab, at Mayo Clinic, CLIA #03D2113087.**

5. Describe the assay: -

   A. Specify the analyte(s), technical platform, and sources of assay components (e.g., reagents, chips, and calibrators). **The technical platform is the Nanostring**

nCounter system, which is FDA-cleared for use with the ProSigna breast cancer assay. The RNA extraction kits are commercially available from Roche. The 64 fluorescently-labeled tags used in the assay will be from NanoString. The positive control is an equimolar mixture of oligonucleotides with complimentary sequences to all probes in Lymph3Cx assay. The oligonucleotides will be purchased in bulk, lyophilized, reconstituted into stock solutions, and pre-mixed by Integrated DNA Technologies similar to our prior work with the Lymph2Cx assay (D. Scott et al, Blood 2014). We have a standard operating procedure for storage and dilution of this calibration standard, which has been used for normalization in all subsequent studies including the proposed trial. Additional PMBCL cell line pellets will be included as positive controls for the Lymph3Cx as well. The analysis algorithm is held behind a firewall on a password protected, NCI-sponsored website, so as to prevent any "drift" or tweaking.

B. Describe the specimens, and anticipated methods for specimen acquisition, fixation or stabilization, and processing. Provide justification for the timing of specimen collection. Describe the scoring procedures and type of data to be acquired:
   - quantitative/continuously distributed
   - semi-quantitative/ordered categorical
   - qualitative/non-ordered categorical

   The specimens will be formalin fixed, paraffin embedded (FFPE) tissue sections from the diagnostic pre-treatment biopsies of the patients, processed under standard clinical protocols at each participating site. Quantitative digital data will be generated from the nCounter system then uploaded to an NCI sponsored website with the analysis algorithm, which will calculate a probability score and assign the results into PMBCL, not PMBCL, or uncertain, and then 3 DLBCL/not PMBCL categories: DLBCL-ABC, DLBCL-GCB, or DLBCL-UNC. The average raw count of the housekeeping genes in the assay is used as a final quality control marker – samples with <80 counts for this metric are reported as "Poor Quality".

A. Provide data on the analytical performance of the assay. -For *in vitro* tests, describe the current status of studies defining the accuracy, precision, reportable range, reference ranges/intervals (normal values), turn-around time and failure rate of the assay as it is to be performed in the trial. Describe the use of positive and negative controls, calibrators, and reference standards for clinical assays. Describe any critical pre-analytic variables. For guidance on regulatory requirements for laboratory assays please visit: http://www.cms.gov/CLIA/05_CLIA_Brochures.asp

   Standard operating procedures (SOPs) for the Lymph3Cx assay have been established as presented at the recent International Conference on Malignant Lymphoma meeting in Lugano, Italy, June 14-17, 2017 (A. Mottok et al. ICML 2017, manuscript under preparation for submission). The assay yielded GEP data of sufficient quality in 157/166 cases (94.6%). The Rimsza laboratory provided the intra- and inter-laboratory reproducibility data for the Lymph3Cx

assay, which was 100% for repeat samples within the same laboratory and between laboratories respectively. The laboratory turn-around time for the assay is 2.5 days from the receipt of tissue sections including RNA extraction, overnight hybridization, digital scanning, and data analysis. There is no reference range. The results are provided as a probability score of classification. The failure rate of the assay in the first 119 cases was 0% (all biopsies yielded sufficient RNA when assessed for pre-analytical variables as described below) using standard chemistry. A positive and negative control and up to ten samples can be included in each 12-well cassette. Positive controls include the mixture of oligonucleotides and cell lines which hybridize with all probes in the assay. The negative control is a well in the cassette that includes all reagents and probes, but no RNA. An important pre-analytical variable is percentage of tumor, which should be a minimum of 60%. To address this, an H&E stained section of each case will be assessed by Dr. Rimsza, who will estimate tumor purity. If needed, macro-dissection of the tissue sections will be performed to increase tumor content. Input is 1 x 10 micron thick section for a 50mm^2 biopsy. For smaller biopsies, proportionally more sections will be taken. Dr. Rimsza will measure the size of the tumor area and determined the number of needed sections at the same time that she determines the tumor content. A Pathology Quality Assurance form is used to document the tissue input specifics (size/number of needed sections and percent tumor). At this time, only formalin fixed biopsies (not other fixatives) have been assessed. The Pathology reports on the biopsies will be reviewed to determine whether formalin or another fixative was used. A complete validation packet for the Lymph2Cx assay as a laboratory developed test in the clinical Molecular Diagnostics in Arizona Laboratory at the Mayo Clinic was completed in November 2016 with on-going patient testing since that time. The Lymph3Cx clinical laboratory validation is underway and estimated for completion in late 2018. Although not for use in clinical decision making in this proposed trial, the Lymph3Cx assay will be run using the same standardized operating procedures as in the Mayo clinical laboratory. CLIA lab identification number 03D2113087.

B. If the assay will be performed at more than one site, describe how inter-laboratory variability in the measurements listed in 5A above will be assessed. Describe how these sources of variation will be minimized to maintain performance at all sites within acceptable limits and to prevent drift or bias in assay. **Not applicable, all testing will be performed at one site.**

6. Provide data on the clinical utility of the integral/integrated assay as it will be used in the trial:

A. Provide background information that justifies the use of this assay result as a marker for this trial. State the hypothesis and rationale for utilizing the biomarker, with supporting preclinical and clinical data, when available. For example, if the integral marker will be used as a stratification or treatment-determining variable, data

supporting its prognostic or predictive association with a main trial endpoint should be described or referenced.

Note: If the trial objectives include an evaluation of the association of the integral marker with a new clinical endpoint or factor not previously studied, explain how the magnitude of the association or effect will be measured and provide power calculations for any statistical tests that are planned.

The Lymph3Cx assigns the molecular COO subtype of cases of large cell lymphomas into PMBCL and DLBCL subtypes with different phenotypes and genotypes. Meaningful analysis of any clinical trial results need to be correlated with COO status in order to accurately describe the enrolled cohort of patients. Diagnosis of PMBCL is difficult, non-reproducible, and relies heavily on clinical presentation in the mediastinum, however, our research consortium recently described PMBCL-like tumors outside of the mediastinum, and conversely, not every case of large B cell lymphoma occurring in the mediastinum is a PMBCL, but could also be a usual DLBCL that happens to present there. (A. Rosenwald et al, J Exp Med, 2003; J. Yuan et al, Am J Surg Path, 2015). Several assays for COO have been published in the literature. The original methods used snap frozen tissues and the Affymetrix gene expression profiling system, which are now accepted by experts as a "gold standard" for COO classification of DLBCL and PMBCL respectively (G. Wright et al, PNAS 2003; A. Rosenwald J Exp Med 2003); but both are expensive, have a poor turn-around time, and the Affymetrix platform does not perform well with FFPE tissue input. The LLMPP research consortium, beginning with the original "discovery" methods, developed a GEP method that is accurate and useful in FFPE tissues.

B. Describe the expected distribution of the biomarker in the study population. Justify the number of patients and specimens to determine feasibility and to demonstrate that the studies are likely to produce interpretable results.

As per the prior LLMPP publication using GEP on frozen tissues, we expect that 80% of patients with an initial diagnosis of PMBCL will classify as PMBCL using the molecular method with the rest being DLBCL (A. Rosenwald et al, J Exp Med, 2003). As per our prior publications we further expect that the DLBCL will subtype as approximately 50% GCB, 35% ABC, and 15% UNC (S. Kendrick et al, Leuk Lymph 2016). The response rates will be compared to GEP classification to determine whether there is a specific subtype that correlates with treatment response. Given that this is a phase II study, descriptive statistics will be used to explore these COO and treatment associations.

C. If cutpoints will be used, specify the cutpoint(s) and describe how these will be used in the trial. Provide the rationale for the cutpoint(s) selected. What proportion of subjects is expected to have values above and below the proposed assay value cutpoints? What magnitude of effect (e.g., treatment benefit) or outcome (e.g., prognosis) is expected for patients with assay results above and below the proposed cutpoint(s)?

The cut-points for classification are pre-set at a probability score of 10% and 90% as generated from the locked Lymph3Cx algorithm, which was previously trained and validated. The results are first classified into PMBCL or not-PMBCL or an uncertain category. Then the non-PMBCL cases (DLBCL) are further classified into one of 3 subtypes such that DLBCL-ABC (equal to or greater than 90% probability score), germinal center B cell subtype (less than or equal to 10% probability of being an ABC type), and unclassifiable category (for all probabilities between 10-90%). It is expected that 60-70% of DLBCL patients will have the GCB subtype of DLBCL. We do not know if there will be a correlation between PMBCL, DLBCL-GCB or DLBCL-ABC subtype and clinical outcome in this trial. The data will be collected retrospectively for correlation.

D. Describe the conditions under which treating physicians and or patients will be able to access the biomarker assay results.
The treating physicians will not have access to these biomarker results, only the Principal Investigator will have access and then only after the clinical trial has completed accrual. The patients will not have access to the results at any time.

Appendix H: Shipping Manifest for Lymph3Cx Cell-of-Origin (COO) molecular subtyping assay

Sample Shipping Manifest for Clinical Research Studies - Single Subject F6.21.0021 v001 — Release Date: 03/18/2019

Sample Shipping Manifest for Clinical Research Studies - Single Subject

Content Applies To: Mayo Clinic Arizona: Molecular Diagnostics - Arizona Lab (MDAZL), Divisions of Anatomic Pathology and Hematopathology

Form Usage: Please complete all fields in "Shipping Site" section, all fields are mandatory. Enter "N/A" in the Comments space if is to be left blank (initial and date). Page 1 is the cover sheet, page 2 contains the sample manifest. **Manifest rows to be left empty should have the "N/A" box checked.** Inclusion of block ID is optional in Section ID field, i.e. "A1-12" is block A1, section #12 as given in example. If "Other" is selected from the Biopsy Type drop-down menu, please specify further by typing in that field.

Shipping Site			
Protocol #:		Subject Study ID:	
Shipped From:		Shipped To:	Mayo Clinic Arizona - MDAZL
Tracking #:		Shipment Carrier:	

Shipment Overview - please indicate the number of each of the following included in shipment:					
H&E stained sections:		Unstained sections:		Slide Boxes:	

Please select "Yes" or "No" for the following questions:		
Do the section and box quantities above match the quantity to be sent?	YES	NO
Do the section IDs in the Manifest page match the IDs on the sections to be sent?	YES	NO
The subject has provided informed consent for the main study.	YES	NO
The subject has consented to end-of-study tissue collection for Unknown Future Studies.	YES	NO
The subject has agreed to Biobanking of residual blood/tissues for future health research.	YES	NO
The protocol eligibility criteria have been met and the specimens being shipped are pre-treatment, formalin-fixed paraffin-embedded tissue sections mounted on positively-charged slides, to include an H&E slide cut contiguously to the unstained sections.	YES	NO

Use this space to provide any additional comments:			
Shipped By:		Witness:	
Date Shipped:		Date:	
Signature:		Witness Signature:	

Receiving Site: Mayo Clinic Arizona - MDAZL			
Received By:		Witness:	
Date Received:		Date:	
Signature:		Signature:	

Did the sections arrive undamaged in the shipping box?	YES	NO
Do the number of sections/boxes received match the number of sections/boxes shipped?	YES	NO
Did the section IDs received match the section IDs on the manifest?	YES	NO

Please explain any "No" answers, or use this space to provide any additional comments:

Sample Shipping Manifest for Clinical Research Studies - Single Subject
F6.21.0021 v001

Release Date: 03/18/2019

Sample Manifest								
Slide Type (Check N/A if row is to be left blank) N/A?		Subject Study ID	Section ID	Date of Consent	Box Number	Thickness (µm)	Biopsy Type (Drop-Down)	Rec'd ?

RELATED DOCUMENTS:

Document/Form Title	Document Identification/Location
	DOCMAN

REVISION / DOCUMENT HISTORY:

Effective Date	Version	Synopsis of Change
03/18/2019	001	New Document (cr)

REVIEW AND APPROVAL SIGNATURES:

Version 001
Reviewer/Date
Primary Approver/Date

Content Information

Content ID (#): F6.21.0021	Release Date: 03/18/2019
Version: 001	Next Review Date:
Title: Sample Shipping Manifest for Clinical Research Studies - Single Subject	Division: Anatomic Pathology, Hematopathology
Workflow Reviewer: Colleen Ramsower	Document Type: Form
Workflow Approver: Lisa Rimsza	Category: MDAZL Forms - Clinical Research
Work Unit: MDAZL	

Appendix I: Blood Collection Kit Mayo Clinic Lymphoma Laboratory

Specimen Checklist and Shipping Instructions

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- 10ml EDTA (purple top) collection tube
- 10ml Red Top collection tube
- 10ml Streck Cell-Free DNA collection tube
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

- Collect the following specimens:
  - Peripheral blood – **Draw appropriate tubes per time point:**
    - 10ml in one (1) EDTA tube
    - 10ml in one (1) Red Top tube
    - 10ml in one (1) Streck Cell-Free DNA tube
- All specimens are to be clearly labeled with the protocol MC1787, the patient's initials (last, first, middle), study patient ID number (if available) and date of collection.
- Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
- Place the filled specimen bag in the Styrofoam container.
- Loosely pack with paper toweling.
- Place the Styrofoam container and Patient Information form within the cardboard mailing sleeve.
- Prepare the package for shipping, applying packing tape as needed. Adhere the Fed Ex Airbill to the exterior of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location. Please e-mail Kim Henderson at Henderson.kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the protocol number MC1787/10193, the Fed Ex tracking number, name and phone number of the contact person. The samples should be shipped to the following:

Mayo Clinic
Attn: Stacey Lehman
221 4th Avenue SW
613 Stabile
Rochester, MN 55905

Patient Information Form

Specimen Date: / /

Patient Initials (last name, first name): _____

Mayo Clinic Number: _____

Protocol #: MC1787/10193

Contact Person: _____

Institution: _____

Address: _____

City State Zip

Phone #: _____

Please indicate which sample time point is being shipped:

1. Baseline
2. Cycle 1 Day 8
3. Cycle 1 Day 15
4. Cycle 3
5. Cycle 4
6. At time of PMD
7. At time of Progressive Disease

Any questions concerning these samples or to obtain blood collection kits for the MC1787/10193 study, please contact:

Stacey Lehman
Mayo Clinic
(507)284-3805

Lehman.stacey@mayo.edu

Affiliates who anticipate participating in this study should please e-mail in advance for kits. Please include the site address, contact information and number of kits being requested.