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Phase 1 Study of Copanlisib with Dose-adjusted EPOCH-R in Relapsed and Refractory Burkitt Lymphoma and other High-Grade B-cell Lymphomas

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Drug Name:	Copanlisib	Etoposide, Doxorubicin, Vincristine, Prednisone, Cyclophosphamide, Rituximab
IND Number:	141280	
Sponsor:	Center for Cancer Research, NCI	Center for Cancer Research, NCI
Manufacturer:	Bayer Pharmaceuticals	Generic
Supplier:	Bayer Pharmaceuticals	CC Pharmacy

PRÉCIS

Background:

- Burkitt Lymphoma (BL) is a highly aggressive B-cell lymphoma that often involves the bone marrow and central nervous system (CNS)
- Frontline therapy cures 80-85% of adults with BL but patients with CNS involvement or those who relapse after frontline therapy are at high risk for treatment failure
- Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of aggressive B-cell lymphomas that are successfully cured by frontline therapy in 60-70% of cases
- A subset of DLBCL that have *MYC* gene rearrangement as well as those that have transformed from an underlying indolent lymphoma have a lower cure rate
- Dose-adjusted (DA)-EPOCH-R is an infusional chemotherapy platform often used as frontline therapy for these aggressive B-cell lymphomas and is an effective chemotherapy platform from which to rationally design novel therapies for patients with BL, high grade B-cell lymphomas- double hit/triple hit (HGBCL-DH/TH), DLBCL and *MYC* rearrangements, and other high-risk DLBCL
- The phosphoinositide 3-kinase (PI3K) pathway is an important signaling pathway for cellular responses to growth factors and a downstream event of B-cell receptor signaling.
- Copanlisib targets both PI3K-α and PI3K-δ isoforms and is approved for relapsed FL, active as monotherapy in DLBCL, and highly effective in pre-clinical models of BL
- Copanlisib crosses the blood brain barrier suggesting it may prevent secondary CNS spread in highly aggressive B-cell lymphomas.
- Copanlisib is a rational targeted agent to be added to DA-EPOCH-R in patients with BL, HGBCL-DH/TH, and other high-risk B-cell lymphomas.

Objective:

- To determine the Maximal tolerated dose (MTD) and Recommended Phase II dose (RP2D) of copanlisib in combination with DA-EPOCH-R in subjects with Burkitt lymphoma (BL) and high grade B-cell lymphomas- double hit/triple hit (HGBCL-DH/TH) relapsed after or refractory to chemo-immunotherapy

Eligibility:

- Subjects must have a histologic diagnosis, confirmed by the Laboratory of Pathology, NCI with one of the following subtypes and prior therapy, as follows:
    - Burkitt lymphoma, Burkitt-like lymphoma with 11q aberration, High-grade B-cell lymphoma, NOS, High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements – following at least 1 anthracycline-containing regimen
      OR
    - DLBCL, NOS, Germinal center B-cell type (GCB) type, T-cell/histocyte-rich large B-cell lymphoma, following at least 1 anthracycline-containing regimen of the 2 prior regimens OR be primary refractory to frontline therapy
- Age ≥ 18
- ECOG performance status 0-2
- Adequate bone marrow and organ function

Design:

- Phase 1, open-label, single center, non-randomized

- "3+3" dosing will be used to determine the RP2D and MTD of dose escalated copanlisib in combination with DA-EPOCH-R
- Maximum 6 cycles (21-day cycles) of combination therapy
- Dose expansion at the RP2D or MTD to evaluate efficacy and further evaluate safety
- To explore all dose levels, including further evaluation in dose expansion cohort, the accrual ceiling will be set at 39

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

1 INTRODUCTION

STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the Recommended Phase II dose (RP2D) and Maximal tolerated dose (MTD) of copanlisib in combination with DA-EPOCH-R in subjects with Burkitt lymphoma (BL) and high grade B-cell lymphomas- double hit/triple hit (HGBCL-DH/TH) who have relapsed after or are refractory to chemo-immunotherapy

1.1.2 Secondary Objectives

- To assess the safety and tolerability of the combination of copanlisib and DA-EPOCH-R in subjects with BL and HGBCL-DH/TH relapsed after or refractory to chemo-immunotherapy
- To determine the complete response rate at the end of therapy, based on Lugano Criteria of the combination of copanlisib and DA-EPOCH-R in subjects with BL and HGBCL-DH/TH relapsed after or refractory to chemo-immunotherapy
- To assess progression free survival (PFS), event-free survival (EFS) and overall survival (OS) of subjects treated with the combination of copanlisib and DA-EPOCH-R in subjects with BL and HGBCL-DH/TH relapsed after or refractory to chemo-immunotherapy

1.1.3 Exploratory Objectives

- To explore the molecular correlates of resistance to copanlisib with DA-EPOCH-R
- To determine role of circulating tumor DNA to monitor response at the end of therapy
- To determine the ability of circulating tumor DNA to predict disease relapse during surveillance after therapy is complete
- To explore the pharmacokinetics of copanlisib in plasma and cerebrospinal fluid (CSF) samples

BACKGROUND AND RATIONALE

1.1.4 Dose adjusted-EPOCH-R in Burkitt Lymphoma (BL)

Burkitt lymphoma (BL) is a highly aggressive B-cell lymphoma characterized by rapidly dividing malignant cells that may involve the bone marrow and/or central nervous system (CNS) (1, 2). It is the most common B-cell lymphoma in children, but accounts for only 1-2% of adult lymphoma (3, 4), except in the setting of HIV where BL reflects 25% of all non-Hodgkin lymphoma (NHL) cases. BL is curable with frontline therapy that includes highly dose-intensive chemotherapy regimens developed in children and young adults with acute leukemias, but cure rates decline with advancing age (5-10). Further, virtually all patients with BL who relapse after frontline therapy with highly dose intensive pediatric regimens will succumb to the disease as salvage chemotherapy is nearly universally ineffective (11).

We have demonstrated dose-adjusted (DA)-EPOCH-R (infusional etoposide, doxorubicin, and vincristine with prednisone, cyclophosphamide and rituximab) is an effective frontline therapy for adults with BL that maintains efficacy with reduced toxicity compared to other regimens. The infusional chemotherapy platform utilized with DA-EPOCH-R is based on the hypothesis that drug exposure time and not peak concentration is the relevant pharmacodynamic principle to optimize

the cell death of rapidly proliferating tumor cells (12). In a pilot study of 30 adult patients with untreated BL, nearly all patients were cured with DA-EPOCH-R (13). These results were confirmed in a multicenter study of risk-adapted therapy in 113 adult patients with untreated BL (14). In this study, the median age was 49 years (range 18-86) and 62% of patients were 40 years or older. After a median follow-up of 59 months, the event-free survival (EFS) and overall survival (OS) for the entire group was 84.5% and 87.0%, respectively. All patients with low-risk BL were cured of disease while the EFS of high-risk patients was 82.1%. In determining risk factors for primary treatment failure, age groups and HIV status did not predict outcomes, but the presence of disease involving the bone marrow (BM), cerebrospinal fluid (CSF), and/or peripheral blood was associated with reduced survival. Deaths on study were equally distributed between disease progression and toxic deaths suggesting that intensification of chemotherapy alone is unlikely to improve outcomes. Further, only 2 of 9 (22%) patients who relapsed after DA-EPOCH-R remained alive after successful salvage therapy. Nearly all patients with relapsed or refractory BL died of disease. Thus, despite the high cure rates of BL patients with frontline therapies, improved treatment strategies are clearly needed for patients with involvement of the bone marrow or CSF and all BL patients who relapse after frontline therapy.

1.1.5 Dose adjusted-EPOCH-R in Diffuse Large B-cell Lymphoma (DLBCL)

DLBCL encompasses a group of aggressive B-cell NHLs with striking genetic heterogeneity and variable clinical presentations. Even though frontline therapy successfully cures ~75% of DLBCL cases, patients with early progression or refractory disease have an OS of only 6 months and are often the focus of clinical trials testing novel strategies (15). The molecular heterogeneity of DLBCL was initially revealed using gene-expression profiling (GEP) in which molecular subtypes of lymphoma emerged with gene expression patterns similar to germinal center B-cells (GCB) or activated B-cells (ABC) and thus the classification system became known as “cell of origin” (COO). The minority of tumors that could not be classified as ABC or GCB cases were called unclassified (16-18). Overall, GCB DLBCL has a better prognosis than ABC DLBCL, but specific subsets of GCB DLBCL are at high-risk for treatment failure (19).

The COO classification identifies DLBCL subtypes that arise from B-cells at different stages of development, that utilize distinct oncogenic mechanisms for survival signaling, and that have dramatically different survival outcomes in response to standard therapies (17, 20, 21). GCB DLBCL arises from B-cells with the gene expression program of normal germinal center B-cells and frequently express the cell surface marker CD10 (18, 22). ABC DLBCL arises from post-germinal center B cells, shares a gene expression program with “activated” B-cells and is characterized by constitutive activation of the NF-κB pathway (23, 24). Up to 20% remain unclassified and rare histologic subtypes like T-cell/histiocyte-rich large B-cell lymphoma are not captured by COO classification.

The 2016 revision of the World Health Organization (WHO) classification recognized ABC DLBCL and GCB DLBCL as distinct molecular subtypes of DLBCL. Further, approximately 10-15% of patients with untreated DLBCL have a rearrangement of the *MYC* oncogene and the WHO classification defined a new subset of high-grade DLBCL based on the presence of rearranged *MYC* and *BCL-2* and/or *BCL-6* [HGBCL-double hit/triple hit 9DH/TH], and is present in approximately 8% of DLBCL (25, 26). HGBCL-DH/TH with *BCL2* rearrangements are all classified as GCB DLBCL (27). HGBCL-DH/TH is not a distinct biologic entity, but identifies subsets of DLBCL at risk for treatment failure with R-CHOP.

A recent study analyzed RNA sequencing data from 157 patients with GCB DLBCL and established a gene expression signature (DHITsig) of 104 genes that identifies 27% of GCB DLBCL with a 5-year time to progression rate of 57% compared to 81% (HR 2.8, *P*<0.001) for other GCB DLBCL cases after R-CHOP (27). The outcomes in this DHITsig GCB DLBCL subgroup were similar to ABC DLBCL. The DHIT signature robustly identifies HGBCL-DH/TH with *BCL2* rearrangements, but they account for only 50% of the high-risk group. A follow-up study with whole genome sequencing demonstrated that high-risk GCB DLBCL by DHITsig may have cryptic rearrangements of *MYC* or *BCL2* not detectable by routine testing (28). In another study of 400 patients with DLBCL, a molecular high grade (MHG) gene expression signature identified 83 (9%) patients with a 3-year PFS of only 37% (95% CI, 24-55) compared to 72% (95% CI, 68-77) for those without the signature (29). Interestingly, 75 (90%) of the patients classified with the MHG signature were GCB DLBCL. Taken together, these studies clearly identify cases of GCB DLBCL that are at high risk for treatment failure after R-CHOP and need novel therapeutic approaches.

We performed the only prospective clinical trial in patients with DLBCL and *MYC* rearrangements. In this multicenter prospective study, DA-EPOCH-R was given for up to 6 cycles in 53 patients with HGBCL-DH/TH (45%), HGBCL (19%), and DLBCL and *MYC* rearrangements (34%) (30). After a median follow-up of 55.6 months, the 4-year EFS was 71.0% (95% CI, 56-81) with an 4-year OS of 76.7% (95% CI, 63-86). No difference in outcome was observed between HGBCL-DH/TH and DLBCL with *MYC* rearrangements, but patients with high-risk IPI scores had an inferior outcome.

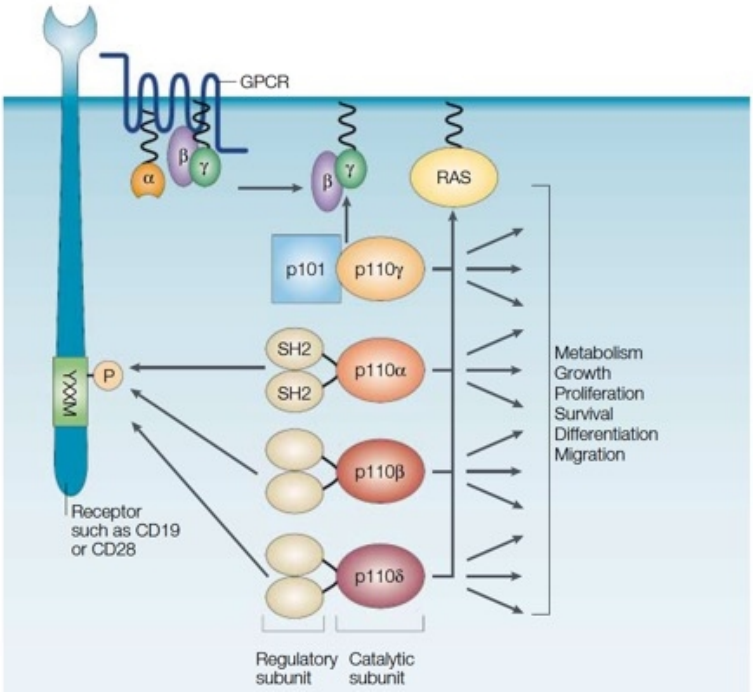
Taken together, these results demonstrate a subset of GCB DLBCL are at high risk for treatment failure and are not completely captured within the new entity HGBCL-DH/TH. DA-EPOCH-R is the most effective chemotherapy platform on which to add rational targeted agents for patients with HGBCL-DH/TH, DLBCL and *MYC* rearrangements, and other high-risk GCB DLBCL.

1.1.6 Phosphoinositide 3-kinase (PI3K) pathway as a therapeutic target

The phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) pathway, also known as the AKT signaling pathway, holds a central role for normal cellular responses to growth factors and cellular homeostasis(31, 32). As a consequence, aberrant activation of the PI3K pathway enhances cell survival and proliferation, thereby leading to malignant transformation across a variety of cancers.

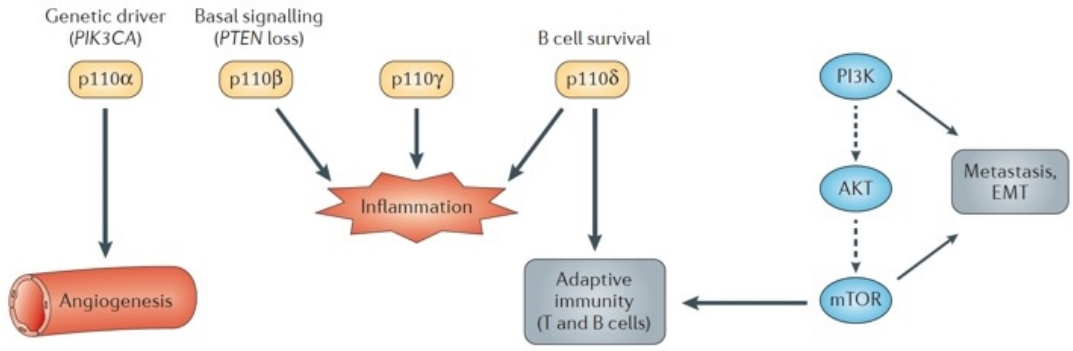
Human cells express three classes of PI3K enzymes and mammals express four class I catalytic isoforms (p110α, β, γ, and δ). Class IA PI3Ks are heterodimeric enzymes consisting of regulatory p85 and catalytic p110 subunits and are primarily responsible for phosphorylating the second messenger, phosphatidylinositol 4,5-bisphosphate (PIP2) (**Figure 1**). Redundancy exists since each of the catalytic subunits can bind to each of the regulatory subunits and different heterodimers are recruited to the same receptors(33). p110α and p110β are ubiquitously expressed in various tissues, p110γ and p110δ are predominantly expressed in leucocytes and hence are attractive drug targets for lymphoid malignancies (34).

Figure 1: Class IA PI3Ks enzymes



P110α is the only PI3K catalytic subunit isoform that is significantly associated with cancer-associated somatic mutations in its gene, *PIK3CA*(35), but other mechanisms of PI3K activation exist including the loss of the tumor suppressor, phosphatase and tensin homolog gene, *PTEN*(36). Further, class I PI3Ks are involved in the recruitment of a number of specific proteins to membrane-signaling complexes, and PI3K effectors including serine/threonine kinases of the AKT family, tyrosine kinases of the TEC family (ITK, BTK, etc.), as well as mTORC1 and mTORC2(32). In this way, multiple downstream signaling pathways can be triggered by PI3K activation. The pathway also contributes to cancer-promoting aspects of the tumor microenvironment including angiogenesis and immune cell crosstalk (**Figure 2**).

Figure 2: PI3K activation pathway



Due to its central role in multiple malignancies, a number of agents have been developed that target the various PI3K isoforms. However, since the PI3K pathway is important for the regulation of a variety of physiological processes in virtually all tissues types, the clinical development of targeted

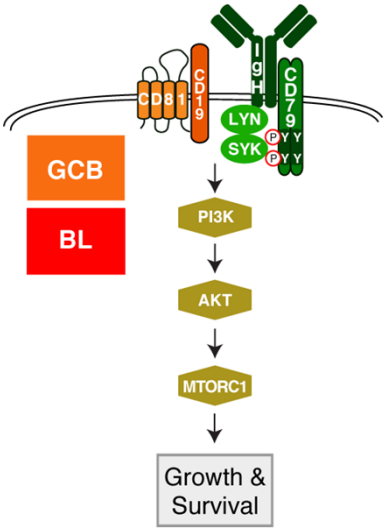
PI3K inhibitors has been slowed by the emergence of dose-limiting toxicities and on-target adverse events.

Among the PI3K isoforms, p110δ plays the most decisive role in B-cell function. Mice harboring PIK3CD deletions show decreased number of mature B cells in the bone marrow and a significant decrease in B cells residing in marginal zone and pleural/peritoneal cavities. PIK3CD depleted B-cells do not proliferate in vitro in response to BCR or CD40 signal and exhibit increased susceptibility to apoptosis and impaired humoral T-cell dependent and T-cell independent responses (37) p110δ inactivation in mice also had protective effect against a broad range of cancers, including non-hematological solid tumors, through interruption of tumor induced immune tolerance and rejuvenation of cytotoxic CD8 (+) T-cells (38).

1.1.7 Scientific Rationale for Targeting PI3K in Burkitt lymphoma and High-risk GCB DLBCL

In the current molecular era of disease definition, precision medicine strategies aim to add rational agents targeting oncogenic drivers to effective chemotherapy combinations (39). Our clinical and translational research teams at the NCI characterize aberrant intracellular signaling pathways within distinct lymphoma subtypes and develop treatment combinations designed to overcome treatment resistance. Pathogenic B-cell receptor (BCR) signaling is a universal feature of aggressive B-cell lymphomas, but different modes of BCR signaling are present within different molecular subtypes. Targeting these subtype specific modes of BCR signaling with rationally designed therapeutics has proven to benefit some of the highest risk group patients that have been refractory to standard immunochemotherapy regimens (40). Thus, defining the mechanisms underlying survival signaling is of critical importance and could lead to novel therapeutic strategies in other high-risk subtypes of lymphoma. We have recently identified novel modes of antigen-independent BCR signaling ("toncogenic BCR signaling") in BL and GCB DLBCL that signal through the phosphatidylinositol 3-kinase (PI3K) pathway to activate AKT and mTOR (**Figure 3**) (41-43). Clinical trials testing various novel agents are now needed to better define the therapeutic potential of targeting BCR signaling in these lymphomas.

Figure 3:Toncogenic BCR Signaling



The normal germinal center B-cell is the presumed cell of origin for both BL and GCB DLBCL, but the genetic profiles of these tumors are distinct (**Figure 4**), suggesting they arise from subtly different progenitors. In over 70% of sporadic cases of BL, mutations in *TCF3,* or its negative

regulator *ID3,* have been identified (**Figure 4**). Functional studies demonstrated that BL cell lines were dependent upon TCF3 expression to control BCR and PI3K activation by repressing a negative regulator of BCR signaling, PTPN6 (42). Further evidence supported these claims by demonstrating a similar loss of PI3K activity upon knockdown of BCR subunits (CD79A and SYK,) overexpression of PTPN6, or treatment with pan-PI3K inhibitors. Importantly, gene expression signatures defined in BL cell lines upon treatment with inhibitors of this pathway were found to be highly expressed in tumor samples from BL patients.

Notably, an oncogenic role for the BCR has long been appreciated in ABC DLBCL, yet the same techniques that elucidated an oncogenic role in ABC and BL were insufficient to identify a role for the BCR in GCB DLBCL. However, recent genome-wide CRISPR-Cas9 genetic knockout screens have changed this notion by demonstrating that similar to BL, GCB DLBCL also utilizes components of proximal BCR signaling such as CD79A, CD79B, SYK, LYN, CD19, and CD81 to maintain PI3K and AKT activity (**Figure 5** and data not shown) (44). The differences in sensitivity to knockdown vs knockout of BCR genes may have to do with different thresholds of BCR expression needed to initiate antigen-independent signaling from the IgM vs the IgG BCRs found in each respective disease. Yet, in both GCB DLBCL and BL, this oncogenic mode of BCR signaling was found to independent of NF-κB (as in ABC DLBCL), and instead, relied heavily on the PI3K/AKT/mTOR pathways and it was highly sensitive to PI3K and mTOR inhibitors. Taken together, our investigations into BCR signaling in aggressive human lymphomas have demonstrated that much like normal B cells, most oncogenic B cells also require their BCR to survive. However, each malignancy has evolved grossly (ABC) or subtly (GCB vs BL) different oncogenic mechanisms to coopt this dominant survival pathway. Our data not only define how this prevalent oncogene (the BCR) functions across aggressive lymphoma subtypes, but also suggests novel therapeutic targets that will be effective in subsets of BL and GCB DLBCL patients.

Figure 4. Distinct Genetic Profiles of BL and GCB and ABC DLBCL

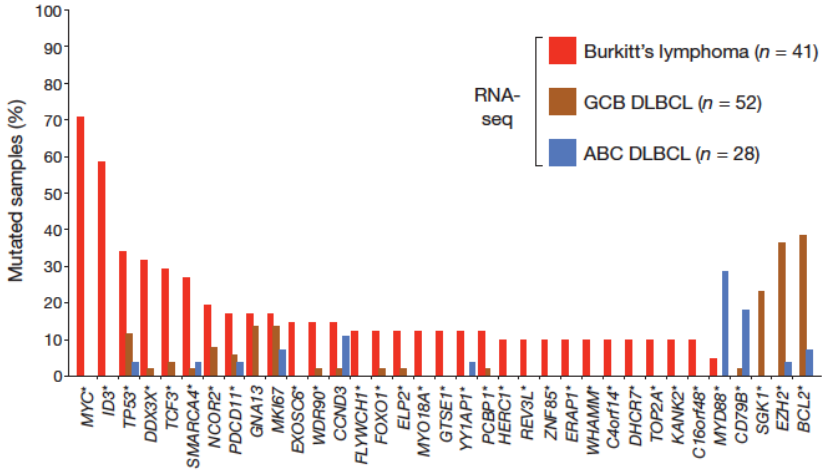
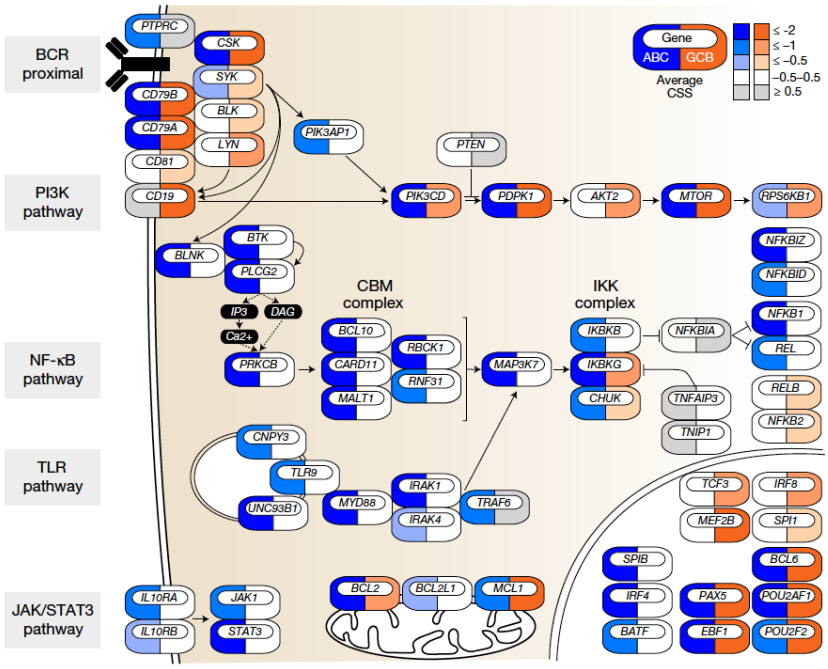


Figure 5. Genes Essential for Oncogenic Signaling in Lymphoma



1.1.8 Copanlisib (Aliqopa®) for High-risk GCB DLBCL and Burkitt lymphoma

Copanlisib (Aliqopa®) is an intraveneous pan-class I PI3K inhibitor with predominant activity against the PI3K-α and PI3K-δ isoforms. Copanlisib uses an intermittent dosing schedule designed to achieve optimal target inhibition within the tumor while sparing normal tissue. Indeed, the strategy of intermittent dosing was more effective in mice bearing breast cancer xenografts than continuous dosing (45). Another potential benefit of simultaneous targeting the PI3K-α isoform is that upregulation of alternative isoforms over time may be a mechanism of resistance to selective PI3K-δ inhibitors (46, 47). Studies in mantle cell lymphoma cell lines and from patient samples have shown that p110α expression increased significantly upon relapse after treatment with idelalisib, suggesting p100α plays a mechanistic role in resistance. In addition, combined inhibition of both p110-α and p110-δ isoforms was a more effective strategy for inhibiting constitutive PI3K activation in cell lines (46). Copanlisib has been studied as monotherapy in DLBCL and demonstrated an overall response rate of 25%, including complete responses in relapsed and refractory cases (48). Further, recent data demonstrates that copanlisib effectively crosses the blood brain barrier suggesting it may prevent secondary CNS spread in highly aggressive B-cell lymphomas (49). CNS safety pharmacology studies of copanlisib in rats showed behavioral abnormalities such as stereotypic licking, swaying gait, vocalization upon touch, and reduced muscle tone beginning about 0.5 hours after a dose ≥18 mg/m2. At doses of 54 mg/m^2, additional CNS effects of piloerection, ptosis, salivation, played limbs, backward walking, stereotypic chewing, hypoactivity, and delayed hot-plate response were noted. These effects indicate moderate CNS penetration of copanlisib. These data demonstrate that copanlisib has activity as monotherapy in aggressive B-cell lymphomas such as DLBCL, including those with CNS involvement.

No clinical activity has been demonstrated for copanlisib monotherapy in patients with relapsed and refractory BL. However, BL is a rare tumor in adults making up only 1-2% of all lymphomas

diagnosed and an estimated 400 cases annually in the United States. The rarity of the tumor coupled with the high cure rate to frontline therapy results in a paucity of prospective trials in relapsed BL.

1.1.9 Copanlisib combined with chemotherapy for B-cell lymphomas

A phase 1 study added copanlisib to bendamustine and rituximab in 10 patients with relapsed FL (n=7), marginal zone lymphoma (n=1), and lymphoplasmacytic lymphoma n=2). There were no dose-limiting toxicities (DLTs) but there were 4 discontinuations due to drug-related adverse events (3 due to copanlisib + BR and 1 due to BR). The most common treatment related adverse events (AEs) were neutropenia (all grade 80%, Grade ≥ 3 50%), nausea (70%, No gr ≥ 3), thrombocytopenia (60%, Gr ≥ 3 none), and hyperglycemia (60%, Gr ≥ 3 50%). No cases of non-infectious pneumonitis were noted and responses were noted in all 7 evaluable patients indicating tolerability and safety of this combination. Currently, the phase III study CHRONOS-4 is investigating use of copanlisib with standard chemoimmunotherapy (B-R or R-CHOP) and a phase 1 study (NCT04156828) is assessing R-CGD (carboplatin, gemcitabine, and dexamethasone) with copanlisib for R/R grade 3b FL and DLBCL. Preliminary safety-run in data from CHRONOS-4 were presented at European Society of Medical Oncology (ESMO) meeting in September, 2020. In addition, the authors reported safety and efficacy data on 11 patients who received copanlisib in combination with R-CHOP (all with follicular lymphoma; 5 patients at 45 mg and 6 at 60 mg). No DLTs were reported at either dose of copanlisib (45 or 60 mg) in either treatment group. Similar to prior data, the most frequent treatment-emergent adverse events (TEAEs) were hematologic (neutropenia and thrombocytopenia) and on-target effects (hyperglycemia and hypertension). Most common TEAEs in copanlisib + RCHOP cohort were hyperglycemia, hypertension, and neutropenia, which also were the most frequent grade 3 events (64% each). The incidence of serious TEAEs was 20.0% (2/10) in the R-B group and 72.7% (8/11) in the R-CHOP group. The 2 serious TEAEs in the R-B group were eosinophilia and lung infection in 1 patient each. The most common (≥20%) serious TEAE in the R-CHOP group was lung infection in 3 patients (27.3%). Drug-related AEs led to discontinuations in 4 patients in the copanlisib BR group (considered related to copanlisib and bendamustine in 4 patients, and bendamustine in 1 patient) vs 5 patients in the copanlisib RCHOP cohort (considered copanlisib related in 5 patients, including 2 related to copanlisib and R-CHOP). One patient in the RCHOP cohort did experience pneumonitis which was an AE of special interest however no colitis was noted. The combination of copanlisib with chemotherapy exhibited high ORR, 90% in BR group and 100% in RCHOP group (Zinzani et al ESMO 2020).

The original version of this protocol was written to test copanlisib with DA-EPOCH-R in relapsed and refractory germinal center B-cell lymphomas, including Burkitt lymphoma and was written with broad inclusion criteria that allowed prior treatment with CAR-T therapy. Accrual to this study was halted after 2 of the first 5 patients had a DLT related to hematologic toxicity with the regimen. Specifics of these cases are included here:

The first patient was a 66 y/o male with heavily pre-treated diffuse large B-cell lymphoma of germinal center B-cell origin (GCB DLBCL) that had transformed from prior splenic marginal zone lymphoma (SMZL). His prior anti-lymphoma therapies included:

1) 2016: Splenectomy (for SMZL)
2) 2020: R-CHOP x 6 (for DLBCL)
3) 2021: Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, Revlimid (VIPOR) x 2 (on study at NIH)

4) 2021: Radiotherapy 30 Gy + 20 Gy boost to thigh lesion
5) 2021: Bendamustine-Rituximab with Polatuzumab
6) 2021: CAR-19 therapy (Yescarta)
7) 2022: Glofitamab with Gemcitabine, Oxaliplatin and Obinutuzumab on trial
8) 2022: Bispecific CAR-19/20 on trial

At study entry, he was mostly confined to sitting in a chair due to his large lesion affecting his right thigh, but his hematologic parameters were normal with an absolute neutrophil count of 1,670 hemoglobin of 9.3 g/dL, and platelet count of 114,000μL. Nonetheless, given his tenuous clinical situation, it was decided to admit him to the hospital for his treatment. He received 30mg of Copanlisib on day 1 of his regimen as planned along with dose level 1 of EPOCH-R. On day 5 of the first cycle, his ANC had decreased to 400 and his platelet count was 75,000μL. The planned day 5 dose of copanlisib was not given and EPOCH-R was finished as scheduled. Throughout the course of the first cycle, both the ANC remained severely low (under 200) and the platelet count decreased under 20,000 μL requiring platelet transfusions. The ANC did not recover to above 500 until day 17 of the cycle and the platelet count remained < 25,000 μL for over 30 days. Even though the patient had an improved thigh lesion and met criteria for a partial response to treatment, he was removed from study therapy, and these events were considered a dose-limiting toxicity of the regimen. In my opinion, the severe neutropenia and thrombocytopenia were predominantly related to the EPOCH-R regimen, but since he had received 1 dose of copanlisib it could not be excluded as a contributing factor. The patient did not receive any more therapy and died of progressive disease 2 months later.

The second patient was a 59 year old male with heavily pre-treated high-grade B-cell lymphoma, double-hit (HGBL-DH) with MYC and BCL2 rearrangements. His prior anti-lymphoma therapies included:

1) 2021: DA-EPOCH-R x 5 cycles
2) 2021: R-ICE x 2 cycles
3) 2021: Rituximab-Polatuzumab with Bendamustine
4) 2022: Fludarabine/Cytoxan followed by CAR-19 therapy (Yescarta)
5) 2022: Rituximab, Gemcitabine, Oxaliplatin x 2
6) 2022:Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, Revlimid, Polatuzumab x 1

At study entry, he had disease affecting mostly his left arm and his lungs, but his hematologic parameters were normal with an absolute neutrophil count of 8200, a hemoglobin of 9.9 g/dL, and platelet count of 135,000μL. He also was admitted to the hospital to receive his first cycle of study therapy. He received copanlisib 30mg on days 1 and 5 as scheduled along with dose level 1 of EPOCH-R regimen. On day 6 of therapy, he was doing well clinically with an ANC of 1550, a hemoglobin of 11 g/dL, and a platelet count of 39,000μL. He was discharged back home with close monitoring by his local oncologist. On day 8 of his first cycle, his platelets were noted to be less than 25,000μL and his hemoglobin was less than 9g/dL. He was scheduled for transfusions of both platelets and red blood cells. He was also noted to have an ANC of less than 500 despite daily injection of filgrastim. He was admitted to the hospital due to worsening of his left upper extremity edema and left pleural effusion signifying disease progression. After admission, he was transferred to the ICU for blood product support, chest tube placement, and broad-spectrum antibiotics. His ANC was nearly zero and he was treated for sepsis although no blood cultures were positive. He

was intubated and required mechanical ventilation for progressive hypoxic respiratory failure due to disease progression. Given his lack of response to therapy, the patient was made DNR/DNI and was terminally extubated in the hospital. He died shortly afterwards. The event was recorded as grade 4 neutropenia and thrombocytopenia attributed to the EPOCH-R regimen and copanlisib. It was felt by the PI and sponsor that the most proximate cause of death was disease progression, but a contribution of toxicity from the regimen could not be fully excluded.

We have previously completed many studies combining novel targeted agents with the EPOCH-R backbone in the relapsed setting, but this one has had unacceptable hematologic toxicity in 2 of the first 5 patients enrolled. In discussions within our Branch and with the safety monitoring committee, we feel that the heavily pre-treated nature of some of the patients that we included along with the fact that they had received prior CAR-T therapy put them at high-risk of these hematologic toxicities. It is our current opinion that it is infeasible to include patients who have received CAR-T in a protocol that includes chemotherapy such as the EPOCH-R backbone. Based on this information, we have amended this study with a change in treatment schedule and eligibility criteria to allow for proper testing of the safety of this regimen.

Copanlisib has been shown to prolong the QT/QTc interval, which may lead to an increased risk for ventricular arrhythmias. For this reason, it is recommended to use copanlisib with caution in patients who have, or may develop prolongation of QT, such as patients with a congenital long QT syndrome, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia.

1.1.10 Study Summary

This is a phase 1 dose escalation study with an expansion cohort of copanlisib in combination with standard dosing of DA-EPOCH-R in subjects with highly-aggressive B-cell lymphomas, such as relapsed BL and high-risk GCB DLBCL. Correlative research for this study will include analyzing the molecular correlates of resistance to copanlisib with DA-EPOCH-R, determining the role of circulating tumor DNA in monitoring response to therapy, and determining the ability of circulating tumor DNA to predict disease relapse. This study will utilize multiplatform genomic analyses of tumor biopsies to identify biomarkers that predict response or resistance. The molecular annotation will include a combination of gene-expression profiling, RNA sequencing, whole-exome sequencing, and identification of copy number abnormalities via array comparative genomic hybridization. Specific aims of these molecular correlates will be based on published literature regarding gene expression and molecular signatures that identify subsets of subjects who are considered high-risk for early treatment failure. Additionally, we aim to identify mechanisms of therapeutic resistance through genomic analysis of circulating tumor DNA and biopsies taken before treatment and at time of clinical progression.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Subjects must have a histologic diagnosis, confirmed by the Laboratory of Pathology, NCI with one of the following subtypes and prior therapy, as follows:

- At least 1 anthracycline-containing regimen:

- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration
- High-grade B-cell lymphoma, NOS
- High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements

OR

- Must have had at least 2 prior regimens, 1 of which must have been anthracycline-containing regimen **OR** be primary refractory to frontline therapy:
  - DLBCL, NOS, Germinal center B-cell type (GCB) type;

    NOTE: subjects with coexisting or a history of indolent lymphoma are eligible (i.e., "transformed lymphoma")
  - T-cell/histocyte-rich large B-cell lymphoma

2.1.1.2 Measurable or evaluable disease on imaging scans or bone marrow

2.1.1.3 No other current systemic anti-lymphoma therapy. **NOTE:** Recent short-term (≤7 days) use of corticosteroids or prior radiation to sites of disease involvement is permitted.

2.1.1.4 Any HIV status will be included in this study as long as infection is controlled; in the opinion of the investigator. Status must be confirmed at screening and the subject must be willing to take any recommended antiretroviral therapy.

2.1.1.5 ≥ 18 years of age on day of signing informed consent

2.1.1.6 ECOG performance status ≤ 2 (see **Appendix A**)

2.1.1.7 Adequate organ function as evidenced by the following laboratory parameters, unless dysfunction is secondary to lymphoma involvement as determined by the investigator:

• Absolute neutrophil count (ANC)	≥ 1,000 /mm^3
• Platelets	≥ 100 x 10^9 /L
• Hemoglobin	≥ 8 g/dL (unless due to disease itself, transfusion permitted to meet criteria)
• Renal function	Glomerular filtration rate (GFR) ≥50ml/min/1.73 m^2 as estimated by Modification of Diet in Renal Disease (MDRD) abbreviated formula. If not on target, a 24-hour urine creatinine clearance can be used to directly measure.
• Total bilirubin	≤ 1.5 x ULN **OR** < 1.5-3.0 x ULN for subjects with liver involvement*
• AST and ALT	≤ 3.0 x ULN **OR** < 5 x ULN for subjects with liver involvement
*Acceptable range as long as there is no persistent nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia	

2.1.1.8 Must have fully recovered from all effects of prior surgery. **NOTE:** Minor procedures requiring "Twilight" sedation, such as tissue biopsies, endoscopies or mediport placement

require a 24-hour waiting period prior to treatment initiation.

2.1.1.9 Women of childbearing potential (WOCBP) and men with female partners of childbearing potential must agree to use a highly effective method of contraception when sexually active (intrauterine device, surgical sterilization, contraceptive rod, abstinence) for the time period between signing of the informed consent form and for at least 1 month after the last dose of copanlisib. WOCBP and men with female partners of childbearing potential must agree to use an effective method of contraception (two of the following: diaphragm, cervical cap, contraceptive sponge, condom, hormonal) when sexually active for the time period between signing of the informed consent and for at least 12 months after the last dose of rituximab. Women of childbearing potential must have a serum pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment.

NOTE: A woman is considered of childbearing potential, (i.e., fertile), following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for continuous 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. The investigator or a designated associate is requested to advise the subject how to achieve highly effective birth control (failure rate of less than 1%), e.g., intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner and sexual abstinence. See **Appendix B** for complete details of acceptable contraceptive methods.

2.1.1.10 Willingness to have a central venous access line placed if the subject does not already have one in place

2.1.1.11 Ability of patient to understand and the willingness to sign a written informed consent document

2.1.2 Exclusion Criteria

2.1.2.1 Subjects previously exposed to, intolerant of, or ineligible for PI3K inhibitors and/or their combination

2.1.2.2 Brain parenchymal involvement

2.1.2.3 Patients who have been treated with prior CAR-T therapy or any regimen containing fludarabine.

2.1.2.4 CMV-positive PCR at screening

2.1.2.5 History of diabetic ketoacidosis

2.1.2.6 Uncontrolled intercurrent illness including, but not limited to the following that may limit interpretation of results or that could increase risk to the subject at the discretion of the investigator:

- Any secondary malignancy that requires active systemic therapy
- Diabetes mellitus with Hgb A1C > 8.5

- Clinically significant interstitial lung disease and/or lung disease that severely impairs lung function
- Uncontrolled HIV
- Active hepatitis C infection. **NOTE:** Subjects who are hepatitis C antibody positive will need to have a negative HCV PCR result before enrollment. Those with a positive PCR for hepatitis C are excluded.
- Active hepatitis B infection. **NOTE:** Patients who are hepatitis B surface antigen (HbsAg) or hepatitis B core antibody (HbcAb) positive will need to have a negative HBV PCR result before enrollment. Those with a positive PCR for hepatitis B are excluded. Those who are hepatitis B surface antigen (HbsAg) or hepatitis B core antibody (HbcAb) positive with a negative PCR for hepatitis B will be treated with antivirals designed to prevent hepatitis B reactivation (e.g., entecavir) throughout therapy and for 12 months after therapy and have monitoring for hepatitis B reactivation with PCR as per Section **3.1.13.2**.
- Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including any of the following:
  - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening
  - Congestive heart failure (New York Heart Association functional classification III-IV)
  - Unstable angina
  - Left Ventricular Ejection Fraction (LVEF) <40% as determined by echocardiogram (ECHO) at screening
  - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third-degree AV block)
  - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
    - Inability to determine the QT interval on screening (QTcF, using Fredericia's correction)
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome
- Known mental or physical illness that would interfere with cooperation with the requirements of the trial or confound the results or interpretation of the results of the trial and, in the opinion of the treating investigator, would make the subject inappropriate for entry into the study.

2.1.2.7 Requirement to continue on any of the medications that are excluded (see Section **0**)

2.1.2.8 Breast-feeding subjects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding

should be discontinued if the mother is treated on study.

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. Study subjects will be recruited from the population of subjects screened in the lymphoid malignancy clinics of the National Institutes of Health. These will include both referrals from outside physicians as well as subject self-referrals. In addition, we participate in a locoregional consortium of eight academic institutions within the mid-Atlantic region that shares information regarding active clinical protocols and aims to enhance subject recruitment across the region.

SCREENING EVALUATION

2.1.4 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.1.5 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the screening consent for this study OR the consent for study 01C0129 (provided the procedure is permitted on that study) on which screening activities will be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a subject has signed the consent.

NOTE: Assessments and procedures to confirm study eligibility should be completed within 28 days prior to treatment (unless otherwise noted). See also the Study Calendar (Section **0**).

2.1.5.1 Clinical Evaluations

- Disease history, including: diagnosis, prior radiation treatment (if applicable), and significant prior/ongoing side effects and symptoms
- Complete medical history, including: all active conditions considered to be clinically significant by the treating investigator
- Physical examination, including: height (screening only), weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status using the ECOG scale

2.1.5.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- CBC with differential

- Chemistry panels (as noted) or specific analyte required for eligibility, including: Creatinine (i.e., or Acute Care Panel); ALT, AST, total and direct (if required) bilirubin (i.e., or Hepatic Panel); serum lipase, and 24-hour urine creatinine clearance (if needed to measure CrCl)
- Urinalysis
- CMV HBV and HCV PCR and HBV serology (within 3 months allowed, also see Section **3.1.13** and **3.1.13.2**)
- HIV antibody (within 3 months allowed)
- Hemoglobin A1C
- Urine and/or serum HCG in women of childbearing potential (within 7 days prior to treatment)

2.1.5.3 Imaging Studies

NOTE: Results from outside NIH are accepted.

- CT chest, abdomen and pelvis with contrast
- PET Imaging (i.e., whole body ^{18}F-FDG PET/CT)
- MRI of brain

2.1.6 Other Procedures

- Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). A tissue sample is required for this evaluation; if archival sample is not available, a fresh tumor biopsy will be obtained.
- Bone marrow aspiration and biopsy (results from outside NIH are accepted)
- Echocardiogram (ECHO) and electrocardiogram (EKG)

SUBJECT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a subject is taken off protocol therapy and when a subject is taken off-study) will take place per CCR SOP ADCR-2, CCR Subject Registration & Status Updates found at

https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.1.7 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) (e.g., laboratory parameter) may be rescreened.

2.1.8 Treatment Assignment Procedures

NOTE: For NCI CCR registration purposes only.

2.1.8.1 Cohorts

Number	Name	Description
1	Dose Escalation	Relapsed/refractory aggressive B-cell lymphomas (see inclusion criteria for subtypes)
2	Dose Expansion	Relapsed/refractory aggressive B-cell lymphoma (see inclusion criteria for subtypes)

2.1.8.2 Arms

Number	Name	Description
1	Dose Escalation, original ***Closed with approval of Amendment 02/22/2023**	Copanlisib (IV) per dose level (30 mg, 45 mg, or 60 mg) on days 1 and 5 of each 21-day cycle in combination with standard dosing DA-EPOCH-R to determine RP2D and MTD of copanlisib. Up to 6 cycles total.
2	Dose Escalation, modified	Copanlisib (IV) per dose level (30 mg, 45 mg, or 60 mg) on day 1 of each 21-day cycle in combination with standard dosing DA-EPOCH-R to determine RP2D and MTD of copanlisib. Up to 6 cycles total.
3	Dose Expansion	Copanlisib (IV) at the RP2D or MTD on day 1 of each 21-day cycle in combination with standard dosing DA-EPOCH-R. Up to 6 cycles total.

2.1.8.3 Arm Assignment

Five subjects in Cohort 1 were enrolled onto Arm 1 which has been closed to enrollment. All future subjects in Cohort 1 will now be assigned to treatment Arm 2. All subjects in Cohort 2 will be assigned to treatment Arm 3.

BASELINE EVALUATION

The baseline evaluations should be performed within 14 days prior to the first dose of copanlisib unless otherwise noted; tests performed as part of screening do not need to be repeated if they were performed within the specified window. See the Study Calendar (Section **0**) for details.

3 STUDY IMPLEMENTATION

STUDY DESIGN

This is a phase 1 dose escalation study with an expansion cohort of copanlisib in combination with standard dosing of DA-EPOCH-R in subjects with highly-aggressive B-cell lymphomas, such as relapsed BL and high-risk GCB DLBCL.

Copanlisib will be administered via IV at escalating doses, with a starting dose of 30mg, on day 1 of each 21-day cycle (see **Table 1** for dose levels and schedule), with a standard 3+3 design for dose escalation. A dose expansion cohort will enroll an additional 10 subjects to be treated at the MTD or RP2D to obtain more safety data as well as initial preliminary efficacy data.

Treatment will continue for a maximum of 6 cycles or until toxicity (i.e., dose limiting toxicity as found in Section **3.1.1** or toxicity requiring discontinuation as defined in Section **0**) or progressive disease. Response evaluation will occur after cycles 1, 3, and 6. After treatment has ended, subjects

undergo follow-up as follows: every 3 months for the first 2 years post-treatment and then every 6 months from years 2-5 post-treatment, and then annually after that. Follow-up is anticipated to end at 5 years post-treatment in the last participant.

3.1.1 Dose Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as: any treatment-emergent, clinically relevant, and related severe (grade ≥ 3) toxicity, i.e., toxicity deemed possibly, probably or definitely related to copanlisib or to the combination therapy, by the PI or designee and occurring during the DLT observation time, defined as Cycle 1 of treatment (i.e., 21 days). Subjects who withdraw before completing DLT assessment for reasons other than a DLT, will not be evaluable for assessment of DLT and will be replaced.

The following toxicities and conditions will be recorded; however, they will not be considered to be DLTs:

3.1.1.1 Non-hematologic AEs

- Grade 3 nausea, vomiting, or diarrhea that persist ≤ 7 days with supportive care
- Grade 3 fatigue
- Grade 3 infection that improves to ≤ grade 2 after initiation of antimicrobials
- Grade 3 electrolyte disturbances that improve to ≤ grade 1 ≤ 7 days with appropriate medical management
- Grade 3 infusion related reaction
- Any grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator to be not clinically significant

3.1.1.2 Hematologic AEs

- Grade 3 or 4 neutropenia that lasts < 7 days. **NOTE:** Grade 3 or 4 febrile neutropenia will only be considered a DLT if the neutropenia lasts ≥7 days
- Grade 3 or 4 thrombocytopenia not associated with significant bleeding and lasts < 7 days
- Grade 3 anemia that is not medically significant
- Grade 3 or 4 lymphopenia

3.1.2 Dose Escalation

Dose escalation for copanlisib will proceed according to the following schedule (**Table 1**) and rules (**Table 2**). Each subject will continue treatment at the dose level on which he/she is enrolled – there will be no intra- subject dose escalation. Subjects may not be enrolled to a new dose level until all subjects treated at the previous dose level have completed the DLT observation period defined in Section **3.1.1**.

Each dose-escalation or de-escalation decision will be documented in the study file. The report, including the supporting safety data and delineation of each criteria met, with the dose-escalation/de-escalation decisions will be provided to and approved by the Sponsor (OSROSafety@nih.gov) before additional participants will initiate study therapy. The Dose Escalation Determination form on the sponsor website: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions may be used for this purpose.

Table 1: Copanlisib Dose Escalation Schedule

Dose Level	Copanlisib
Level 1	30 mg on Day 1
Level 2	45 mg on Day 1
Level 3	60 mg on Day 1

Table 2: Dose Escalation Rules

Number of subjects with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter up to 3 subjects at the next dose level
1 out of 3	Enter up to 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. At least 6 subjects must be entered at the recommended phase 2 dose.

3.1.3 Dose Expansion

Once the last subject enrolled to Cohort 1 Arm 2 completes the first cycle of treatment and the MTD or RP2D is determined, the study will proceed to the dose expansion phase with enrollment of an additional 10 subjects to a Cohort 2 "expansion cohort" to obtain more safety data as well as initial preliminary efficacy data.

As an additional stopping rule for safety, if at any time after 3 subjects have enrolled in the expansion cohort, ≥1/3 subjects cumulatively treated in the expansion are identified as having a DLT, no further subjects will enroll. See also Section **0**.

DRUG ADMINISTRATION

3.1.4 Drug Administration

Each cycle is 21 days (3 weeks). Delays may apply based on toxicities. Treatment can continue for up to 6 cycles.

Treatment will be administered on an outpatient basis during days 1-5 of a cycle, however, may be given as an inpatient for matters of convenience or investigator preference in case of additional monitoring. Reported adverse events and potential risks are described in Section **14**. Appropriate dose modifications are described in Section **0**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

3.1.5 Study Dosing Schema

Drug	Daily Dose	Route	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6-15
Copanlisib	Per dose level	IV	X					No drug(s)
Rituximab	375 mg/m^2	IV	X					
Etoposide	50 mg/m^2	CIVI	X	X	X	X		
Vincristine	0.4 mg/m^2	CIVI	X	X	X	X		
Doxorubicin	10 mg/m^2	CIVI	X	X	X	X		
Cyclophosphamide	750 mg/m^2	IV					X	
Prednisone	60 mg/m^2 BID	Oral	X	X	X	X	X	

3.1.6 Copanlisib

All subjects will receive copanlisib (at a dose based on the dose level they are enrolled to) administered via IV on Day 1 of Cycles 1-6. Dosing is not based upon subject weight (i.e., "fixed" dose). Infusions may be done peripherally or via central venous access device.

Copanlisib will be administered as a 60-minute infusion and prior to EPOCH-R on day 1 of each cycle. Every effort should be made to target the infusion timing as close to 60 minutes as possible; however, a preferred window of -5/+10 minutes to account for variability of infusion pumps is permitted. On infusion days, subject's blood pressure will be monitored at 0 h (pre-dose), 30 (±10) min (mid-infusion), 60 (±10) min (end of infusion) (See Section **3.1.9.5**).

No premedications are required for copanlisib; however, premedications including corticosteroids may be used in specific subjects at treating investigator discretion or as directed per toxicity management.

3.1.7 Dose-adjusted (DA) EPOCH-R Regimen

Study treatment administration for EPOCH-R will take place as outlined in Section **3.1.5**, unless the subject experiences unacceptable toxicity or disease progression. Dose adjustment for subsequent cycles will be determined by the absolute neutrophil count (ANC) or platelet nadir from the previous cycle (whichever is lowest). Subsequent treatment doses are determined by hematological toxicity experienced on the previous cycle (see Section **0** for dose adjustments).

Investigators should refer to prescribing information for storage and handling, and detailed instructions on the administration of rituximab, cyclophosphamide, etoposide, doxorubicin, vincristine, and prednisone. Rituximab biosimilar drugs are not permitted in this study. Biosimilar drugs have not been validated with DA-EPOCH-R in these tumors, therefore, we do not allow

their inclusion. All IV drugs should be administered per local practice. All subjects will receive DA-EPOCH-R and pre-medications for Cycles 1-6 at the following doses:

- EPOCH-R chemotherapy
    - Rituximab 375 mg/m^2 IV per protocol on Day 1 prior to EPOCH agents
    - Vincristine 0.4 mg/m^2/day (no cap) CIVI on Days 1-4* (total 1.6 mg/m^2 96 hours)
    - Doxorubicin 10 mg/m^2/day CIVI on Days 1-4* (total 40 mg/m^2 96 hours)
    - Etoposide 50 mg/m^2/day CIVI on Days 1-4* (total 200 mg/m^2 96 hours)
    - Cyclophosphamide 750 mg/m^2 IV on Day 5 (following infusions)
    - Prednisone 60 mg/m^2 PO BID Days 1-5 (total 120mg/m^2/day)

    ***NOTE:** Taking into account copanlisib administration on day 1, the 96 hours of EPOCH-R administration ends on day 5 of each cycle.

3.1.8 Supportive Medications

NOTE: Supportive and pre-medications may be adjusted at the discretion of the investigator.

3.1.8.1 Premedication

Approximately 30-60 minutes prior to rituximab:

- Acetaminophen 650 mg PO x 1
- Diphenhydramine 50 mg PO x 1

3.1.8.2 CNS prophylaxis

Subjects with active CSF disease will receive methotrexate 12 mg intrathecal (IT) twice weekly until 2 weeks past CSF clears (minimum 8 doses); then, weekly for 6 doses, followed by monthly for 6 doses.

3.1.8.3 Ancillary medications for DA-EPOCH-R

NOTE: Alternative ancillary medications (e.g., H2 blocker) may be used at recommended dosages at discretion of the investigator.

- Pegfilgrastim 6mg subcutaneous injection one time dose on Day 6 or Filgrastim at 300mcg/dose if body weight < 75kg or 480mcg/dose if body weight ≥ 75 kg starting on Day 6 and continued once daily by subcutaneous injection until ANC > 5000/mm^3 after the neutrophil nadir for ALL cycles
- Omeprazole 20 mg/day PO (or equivalent)
- Colace 100mg PO twice daily **OR** Docusate/Senna2-4 tablets QD
- Lactulose 20g PO every 6 hours PRN until resolution for treatment of constipation
- Trimethoprim/sulfamethoxazole DS 1 tablet PO three times weekly (or equivalent if allergic), if indicated
- Entecavir, 0.5mg PO daily, if indicated.

3.1.8.4 Pneumocystis Jiroveci Prophylaxis

All subjects should receive prophylaxis for Pneumocystis Jiroveci during study therapy administration. Trimethoprim/sulfamethoxazole 1 DS tablet by mouth on Monday, Wednesday, and Friday is the preferred schedule.

Subjects allergic to either component may receive inhaled pentamidine 300 mg once a month or other standard treatments. Treatment will begin with initiation of treatment (i.e., Day 1 of the copanlisib) and will be stopped upon completion of therapy unless continued administration beyond this point is deemed necessary based on inadequate immune reconstitution.

3.1.8.5 Antiemetics

Prophylactic anti-emetics may be administered according to standard practice. The routine use of standard antiemetics, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to copanlisib administration will be not allowed.

DOSE MODIFICATIONS

3.1.9 Copanlisib

Adverse events may occur shortly after the first dose of copanlisib and it must be withheld for all drug-related toxicities considered severe or life-threatening as per below. For all AEs/SAEs, the treating investigator may use discretion with regards to dose holds and supportive care. The dose of copanlisib should not be modified during the DLT window. It is recognized that attribution of causality of any AE to the test drug specifically may be difficult. However, in previous trials, certain toxicities were seen only in relation to copanlisib, e.g., transient increases in glucose and blood pressure. Based on this knowledge the investigator may decide on the necessary dose modifications during cycles 2 through 6 as per **Table 3**.

Table 3: Dose levels of copanlisib

Dose level 3:	60 mg of copanlisib
Dose level 2:	45 mg of copanlisib
Dose level 1:	30 mg of copanlisib

For subjects entered onto a starting dose of dose level 1, no dose reductions are allowed, and subjects who do not tolerate copanlisib dose of 30 mg must discontinue study treatment permanently. Subjects who start at dose level 2 may have the dose of copanlisib dose reduced to dose level 1 during cycles 2 through 6 at the discretion of the investigator for toxicities that are probably or definitely related to copanlisib. For subjects who start at dose level 3, they can have the dose of copanlisib dose reduced to dose level 2 during cycles 2 through 6 at the discretion of the investigator for toxicities though probably or definitely related to copanlisib, but cannot be dose reduced to dose level 1. After having fully recovered from the toxicity that led to dose reduction, re-escalation to the original starting dose level will be allowed at the investigator's discretion, with the exception of non-infectious pneumonitis (NIP).

Dosing interruptions are permitted in the case of medical and/or surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays) but should be discouraged. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, whenever possible. The reason for interruption should be documented in the medical/research records.

3.1.9.1 Unacceptable Toxicity – Withdrawal Criteria

- CTCAE Grade 4 hypertension

- CTCAE Grade 4 dermatologic toxicity
- CTCAE Grade ≥ 3 non-infectious pneumonitis
- Persistent post-infusion hyperglycemia despite optimal glucose lowering therapy
- Drug-induced pancreatitis
- Development of a new malignancy. New malignancy will be reported as an SAE, with the serious criterion of "important medical event".
- Severe allergic reaction to study drug (such as CTCAE Grade 3 or 4 hypersensitivity reaction).

3.1.9.2 Hematologic toxicity

Dose modifications and treatment interruptions for copanlisib must be done according to the guidelines in **Table 4**. The investigator may judge a more conservative dose modification appropriate. Therefore, if these guidelines are not followed, the rationale for other measures is to be documented in detail in the subjects's medical record.

Table 4: Dose modification of copanlisib/for hematological toxicity

Hematological toxicity (any of the following)	Study treatment action (for any toxicity)
• CTCAE Grade ≥ 3 thrombocytopenia (platelet < 50,000/mm^3) • Febrile neutropenia [a] • CTCAE Grade ≥ 3 neutropenia (ANC < 1000/mm^3) • CTCAE Grade ≥ 3 anemia (Hb < 8 g/dL)	Delay infusion until criteria displayed in Section **3.1.14** are met. Subject can be treated at one dose level lower at the investigator's discretion. If more dose reductions are required than allowed per protocol, discontinue copanlisib permanently. The lowest dose level is 30 mg.
ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria of Adverse Events; Hb = hemoglobin a: These subjects should recover from neutropenia, without fever	

Neutropenia and febrile neutropenia are listed in the current version of the IB as expected adverse events. If the guidelines given in **Table 4** are not followed, the rationale for other measures is to be documented in detail in the subject's medical record.

3.1.9.3 Non-hematologic toxicity

Dose modification recommendations for non-hematologic toxicities attributable to copanlisib other than glucose increases (Section **3.1.9.6**), non-infectious pneumonitis (Section **3.1.9.4**), and blood pressure increases (Section **3.1.9.5**) are outlined below in **Table 5**. The investigator may judge a more conservative dose modification appropriate. Therefore, if these guidelines are not followed, the rationale for other measures is to be documented in detail in the subject's medical record.

Table 5: Dose modification of copanlisib for non-hematological toxicity*

Toxicity [a]	Occurrence	Study Drug Action	
		For current course of therapy	For next course of therapy
Grade 1-2	Any appearance	No change	No change
Grade 3[b]	1st appearance	Delay until Grade ≤ 2	No change
	2nd appearance	Delay until Grade ≤ 2	Decrease by one dose level [c]
	3rd appearance	Permanently discontinue	
Grade 4	Any appearance	Permanently discontinue	–
Toxicity requiring delay for > 21 days		Permanently discontinue	–

* except glucose increases, dermatologic toxicity, non-infectious pneumonitis and blood pressure increases
a: Toxicities according to CTCAE
b: Despite maximum supportive therapy
c: Not applicable for 30 mg dose level

3.1.9.4 Non-infectious pneumonitis (NIP)

In the event of suspected NIP of any grade, copanlisib must be interrupted and a diagnostic examination of a subject experiencing pulmonary symptoms should be conducted. If NIP is the final diagnosis, copanlisib must be permanently discontinued if CTCAE grade ≥3; for CTCAE grade 2 treat until resolution or ≤ CTCAE 1 and resume copanlisib at a reduced dose (i.e., 1 lower dose level; **Table 3**). If grade 2 NIP recurs or if the subject is already at the lowest dose level of copanlisib, discontinue copanlisib (see **Table 6**). Pneumonitis is to be reported as such only in the event of NIP. Treat NIP with systemic steroids at the discretion of treating investigator. The investigator is requested to differentiate between non-infectious pneumonitis (NIP), and infectious pneumonitis (viral, bacterial, 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.

Table 6: **Dose adjustment in cases of non-infectious pneumonitis (NIP)**

Suspected or confirmed NIP per CTCAE	Action Taken	Re-treatment dose after recovery
Grade 1	No Change	NA
Grade 2	Dose Interruption Until recovery to ≤ grade 1	Decrease dose to the next lowest dose level [a]
Grade 2 second occurrence	Permanent Discontinuation	NA
Grade 3	Permanent Discontinuation	NA
Grade 4	Permanent Discontinuation	NA

a: Not applicable for 30 mg dose level

3.1.9.5 Hypertension

No dose of copanlisib should be given if blood pressure is ≥ 150/90 mmHg. Antihypertensive medication may be given to control the increased blood pressure. Dosing can proceed on the

scheduled day if there are at least 2 consecutive measurements <150/90 mmHg, about 5-10 (+5) minutes apart. Otherwise dosing must be delayed (see **Table 7**).

Subjects with a post-dose blood pressure that may have life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis) must permanently discontinue the study drug.

Table 7: Dose modification of copanlisib for 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 BP measurements about 5-10 (+5) minutes apart returns to < 150/90 mmHg. If BP does not 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]
All other times: • 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 4	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 30mg.

The management of acute blood pressure increases following copanlisib will need to be individualized for each subject, but experience in Phase I has suggested the benefit of dihydropyridine calcium channel blockers (i.e., amlodipine, felodipine). Nitrates should also be considered. In general, it is advisable for investigators to be prepared, so that antihypertensive medication is readily available in case of need.

In the event of the occurrence of hypertension ≥ 150/90 mmHg during infusion of copanlisib at any cycle, antihypertensive treatment is suggested as indicated (**Table 7**). In the event of the occurrence of CTCAE Grade 3 hypertension during infusion of copanlisib, the infusion should be interrupted, and antihypertensive treatment administered. Infusion can be resumed when blood pressure has returned to <150/90 mmHg.

Blood pressure will be measured every 5-10 minutes 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 subject should rest for 5-10 minutes before blood pressure is recorded.

On infusion days, blood pressure will be measured at 0 h (pre-dose), 30 (±10) min after infusion starts (mid-infusion), and 60 (±10) min (end of infusion).

3.1.9.6 Blood glucose

Because of its inhibitory effect on the PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with a temporary increase in blood glucose. Addition of a meal in close proximity to copanlisib infusion may exacerbate glucose increase. It is recommended that timing and content of caloric intake on infusion days is monitored by the investigators. For subjects with type 1 or type 2 diabetes, consultation with an endocrinologist will be done prior to first infusion of copanlisib**.** The investigator will review the glucose profile during and post the copanlisib infusions; see **Table 8** for requirements.

Table 8: Fasting requirements and pre-dose glucose levels

Period	Fasting ≥ 8 h required before first glucose measurement	Pre-dose glucose levels	Fasting required before study drug infusion
Day 1 of each cycle	No	<160 mg/dL (fasting) (8.9 mmol/L) < 200 mg/dL (11.1 mmol/L) (non-fasting or random)	Conditional [a,b,c]

a. The decision regarding meal timing and fasting can be made by the investigator based on glucose response patterns during prior treatment days (see text below regarding meal timing on infusion days for further details).

b. Diabetic subjects who take insulin treatment at any cycle visit:

Timing and content of caloric intake on infusion days will be managed by the investigator. Consultation with treating physician or diabetes/endocrinologist is advised.

c. A small, light low glycemic index meal may be taken at least 4 hours before the start of the copanlisib infusion for subjects who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.

Timing and content of caloric intake on infusion days will be managed by the investigator. Consultation with treating physician or diabetes/endocrinology physician is advised. Post-infusion glucose monitoring will be added in all subjects with pre-existing diabetes mellitus and subjects who have random non-fasting glucose levels exceeding 200mg/dL.

The investigator may manage the timing of post infusion meals based on the glucose profile during prior infusion(s) to minimize glucose increases. This is in addition to glucose lowering medication. Subjects may require home glucose monitoring if hyperglycemia is persistent. The specific type of monitoring will be individualized with consultation from an endocrinologist, but may include pre-meal and post-meal monitoring of blood glucose monitoring.

All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, and meal timing will be collected as part of the clinical source documentation.

NOTE: Caloric intake and timing recommendations for diabetic subjects who require insulin treatment prior to the infusion at any cycle visit should be managed by the investigator based on consultation with treating physician or diabetes/endocrinologist physician.

3.1.9.6.1 Glucose measurements

Cycle 1 Day 1:

Fasting is required (8-hour minimum) only on Cycle 1 Day 1 before the first glucose measurement on date of infusion. A low glycemic index meal may be taken 2 hours post-infusion unless the subjects needs to have a low glycemic meal and is unable to fast for this period of time, then glucose test should be taken prior to meal intake.

All subsequent infusions after Cycle 1 Day 1:
The decision regarding meal timing can be made by the investigator based on glucose response patterns during prior treatment days.

NOTE: If subjects needs to have a low glycemic meal prior to the infusion, then glucose test should be taken prior to the meal and/or at 1-2 hours after the meal.

After Cycle 1 Day 1, a low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for subjects who have their infusions scheduled at a later treatment time or due to their age or medical condition when fasting prior to infusion is not viable.

3.1.9.6.2 Glucose monitoring

Treatment Cycle 1, Day 1:

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

- On Cycle 1 Day 1, subjects should be fasting for at least 8 hours prior to the pre-dose glucose measurement. For details on fasting requirements and glucose measurement during Cycle 1 Day 1 please refer to **Table 8**.
- Blood glucose will be measured prior to infusion either with serum chemistry on the day of infusion or an immediate fingerstick glucose check within 30 minutes pre-dose and subsequently, if clinically indicated at the discretion of the investigator. Subjects should be educated on the signs and symptoms of hyperglycemia, such as frequent urination, increased thirst, blurred vision, headaches and difficulty concentrating and must report these to the investigator or their physician immediately.

All subsequent infusions after Cycle 1 Day 1:
If hyperglycemia noted less than 250 mg/dL on Cycle 1 Day 1, at the discretion of the investigator, post-infusion glucose monitoring may or may not be performed. Pre-infusion glucose test prior to each subsequent infusion either with serum chemistry or an immediate fingerstick glucose check within 30 minutes pre-dose is required to ensure fasting levels less than 160 mg/dL or random/non-fasting glucose levels less than 200 mg/dL.

Glucose monitoring at home:

- For all subjects (who experienced persistent glucose >250 mg/dL (13.9 mmol/L) or received anti-diabetic treatment on the day of infusion), fasting glucose should be measured the next day. If glucose reading is < 100 mg/dL (5.5 mmol/L) (non-diabetic) or < 160 mg/dL (8.9 mmol/L) (diabetic) record and stop further glucose measurements until the next copanlisib infusion. If glucose is > 100 mg/dL (5.5 mmol/L) (non-diabetic) or > 160 mg/dL(8.9 mmol/L) (diabetic), the study nurse or investigator should be informed. If the subject has known diabetes and already monitors his/her blood glucose as part of routine

diabetes care, the routine measurements should not be replaced by the study-specific measurements. In this situation, subjects should add the study-specific measurements to their routine.

- In non-diabetic subjects who experience persisting glucose > 250 mg/dL (13.9mmol/L) or who require treatment to maintain optimal glucose levels; consultation with endocrinologist is recommended. These non-diabetic subjects will be trained how to measure their capillary blood glucose levels at home. If applicable, subjects will be provided with glucose meter and supplies (lancets, test strips and diary) to register measured values and record oral glucose lowering medication and/or insulin administration.

3.1.9.6.3 Management of infusion-related hyperglycemia

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially. Please refer to table below for dose modifications and management of hyperglycemia.

Glucose Increase	Assessment	Management
Asymptomatic glucose increases ≤ 250mg/dL (13.9 mmol/L)	Does not generally require treatment with glucose lowering medication.	Oral Hydration
Glucose increase > 250mg/dL (13.9 mmol/L)	Hydration status should be clinically assessed.	Initiate IV fluids to maintain a urine output of at least 150cc/hour and recheck blood glucose within 4 hours. Consider short acting insulin if glucose persists at > 250 mg/dL (13.9 mmol/L) despite IV fluids or if the subject is symptomatic
Glucose increase > 500mg/dL	Repeat glucose testing every 2-4 hours. If glucose value is decreasing, glucose levels may be followed without glucose lowering medication treatment if hydration status is normal as clinically assessed Consultation with endocrinologist can be considered	Initiate IV fluids to maintain a urine output of at least 150cc/hour and recheck blood glucose within 4 hours. Initiate short acting insulin if glucose persists at > 500 mg/dL (13.9 mmol/L) despite IV fluids or if the subject is symptomatic

3.1.10 Rituximab

There will be no dose reductions for rituximab or prednisone. Rituximab should be held for any grade 3 or 4 toxicity felt to be probably or definitely related to rituximab and clinically significant. Rituximab should be held until the adverse event returns to baseline or resolves. Detailed dosing instructions for infusion reactions are provided in the product label.

3.1.11 EPOCH Modifications

Treatment with EPOCH will be initiated at Dose Level 1 (as shown below). After Cycle 1 of EPOCH-R, subsequent treatment doses for doxorubicin, etoposide, and cyclophosphamide will be based on measurements of the previous cycle ANC or platelet nadir, whichever is lower. Dose adjustments will be based on measurements of twice weekly CBC only, even if additional CBCs are obtained. Dose escalation to higher dose levels applies to doxorubicin, etoposide, and cyclophosphamide but only cyclophosphamide is reduced in dose levels -1 and -2.

3.1.11.1 Dose Levels and Drug Doses for DA-EPOCH-R

The following table describes the dose levels and drug doses for DA-EPOCH-R:

Drug Agents		**Dose Levels and Daily Drug Doses**							
		-2	-1	**1**	2	3	4	5	6
Adjusted Agents	Doxorubicin (mg/m^2/day)	10	10	**10**	12	14.4	17.3	20.7	24.8
	Etoposide (mg/m^2/day)	50	50	**50**	60	72	86.4	103.7	124.4
	Cyclophosphamide (mg/m^2/day)	480	600	**750**	900	1080	1296	1555	1866
Non-Adjusted Agents	Rituximab (mg/m^2/day)	375	375	**375**	375	375	375	375	375
	Vincristine (mg/m^2/day; No cap)	0.4	0.4	**0.4**	0.4	0.4	0.4	0.4	0.4
	Prednisone (mg/m^2 BID)	60	60	**60**	60	60	60	60	60

3.1.11.2 Hematologic Toxicity - Dose Level Adjustments for EPOCH

To begin a cycle, ANC must be ≥1,000 cells/µl and platelets must be ≥75,000 cells/µl. Delay cycle by up to 2 weeks if these values are not met on Day 1 of cycle. Filgrastrim may be used for several days to increase ANC. If delay is greater than 2 weeks, then contact PI.

Event	**Dose Modification**
If Nadir ANC ≥ 500/µl on all measurements	↑ One level above last cycle
If Nadir ANC < 500/µl on 1 or 2 measurements	Same level as last cycle
If Nadir ANC < 500/µl ≥ 3 measurements	↓ One level below last cycle
If nadir platelet < 25,000/µl on ≥ 1 measurement	↓ One level below last cycle

3.1.11.3 Ileus and Constipation

Symptomatic ileus/constipation may occur with vincristine. If ileus or constipation require hospitalization, the next dose of vincristine should be reduced by 25%. If symptoms do not recur at the reduced dose, then the vincristine dose may be re-escalated on subsequent cycles

3.1.11.4 Renal dysfunction

Etoposide should be reduced 25% on cycle one for creatinine clearance < 50 cc/min on the day of starting a new cycle. If the creatinine clearance remains low on subsequent cycles, etoposide should remain at the reduced level as in the previous cycle. Etoposide should be returned to full

dose (or escalated if indicated) once creatinine clearance > 50 cc/min. No other dose modifications for abnormal renal indices will be made for enrolled patients.

3.1.11.5 Hyperbilirubinemia

- Doxorubicin

No doxorubicin dose modifications will be made for increased bilirubin ≤ 7 mg/dL. Doxorubicin should be held for bilirubin > 7 mg/dL, until it returns to ≤ 7 mg/dL.

- Vincristine

Vincristine dose will be decreased for elevated bilirubin according to the following scale:

Bilirubin (mg/dL)	**Vincristine dose**
> 1.5 - < 3.0	Decrease by 25%
≥ 3.0	Decrease by 50%

Vincristine dose can be re-escalated as hyperbilirubinemia improves.

3.1.11.6 Neuropathy

Sensory and motor neuropathy may occur with vincristine. Vincristine doses should only be reduced if the subject develops neuropathy that interferes with activities of daily living. Most vincristine associated neuropathy resolves after treatment completion.

- **Sensory neuropathy:**

Grade	**Vincristine dose (%)**
2	100
3	50
4	0

- **Motor neuropathy**:

Grade	**Vincristine dose (%)**
1	100
2	75
3	25
4	0

If neuropathy resolves to lower grade, doses for that lower grade may be reinstituted at investigator discretion. If the grade of neuropathy increases after being re-escalated, doses must be reduced for the appropriate toxicity grade and may not be re-escalated, even if neuropathy resolves again to a lower grade.

ON STUDY ASSESSMENTS/EVALUATIONS

3.1.12 Description of Evaluations and Procedures

Upon confirmation of eligibility and successful registration, and following completion of the Screening/Baseline visit, subjects will begin treatment with copanlisib. After Cycle 1 of combined copanlisib and DA-EPOCH-R, pre-treatment assessments may be performed up to 3 days prior to

Day 1 of a cycle, except where otherwise noted. The results from all procedures/tests must be reviewed prior to initiation of each cycle of treatment for consideration of dose modifications.

Copanlisib and DA-EPOCH-R will continue until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section **3.1.22**, or a maximum of 6 cycles each 21 days, whichever occurs first.

Refer to the Study Calendar (Section **0**) for the timing of all tests and procedures to be conducted on study/during treatment. The following is a description of all procedures:

For screening procedure details, refer to section **0**. Baseline/C1D1 evaluations do not need to be repeated if performed at screening. All evaluations will be done within 14 days before treatment initiation on Day 1 of Cycle 1 (except for pregnancy test which should be performed within 7 days). If treatment does not start within 28 days after enrollment, screening evaluations will be repeated. For all subsequent cycles, all evaluations are to be done within 3 days of cycle treatment initiation. Dose administration can be delayed by no more than 3 weeks for scheduling conflicts.

The timepoints for assessments are listed in the Study Calendar (Section **0**). The following describes the assessments to be done:

- Physical exam: review of organ systems, weight, and vital signs (i.e., temperature, pulse, respirations, blood pressure). Height will only be required at screening. After initiation of study drug, symptom-directed physical examinations will be performed as clinically indicated in the investigator's judgment.
- Performance status (ECOG): an assessment of activities of daily living; see **Appendix A**.
- Laboratory assessments: the following comprises the required tests/analytes per panel. These may be performed outside NIH and results forwarded to the study team for review and management.
    - CBC with differential: includes Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet.
    - Panels:
        - Acute care panel includes Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR.
        - Hepatic panel includes Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin.
        - Mineral panel includes Albumin, Calcium, Magnesium, Phosphorus.
    - Other: LDH, HBV reactivation monitoring- see Section **3.1.13.**, and CMV reactivation monitoring- see Section **3.1.12**.
    - Hemoglobin A1C
- Pregnancy test: Urine or serum HCG for women of child-bearing potential.
- Urinalysis
- Lumbar puncture- with cytology and flow cytometry if clinically indicated, at the end of treatment only if positive at baseline
- Bone marrow aspiration/biopsy- at the end of treatment only if positive at screening; repeat in follow-up to confirm response or progression.

- Peripheral blood flow cytometry
- CT scans- chest, abdomen and pelvis; may be adjusted to assess additional known sites of disease, as needed.
- 18F-FDG-PET/CT scans
- Study drug administration schedule- see Section **0**
- Adverse events and concomitant medication review: Adverse events and concomitant medication will be continuously monitored throughout the study until disease progression or end of treatment visit. Adverse events that occur beyond 30 days after the last administration will be recorded per **0**.
- Follow-up after treatment: See Section **0**
- Correlative studies: Refer to section **5**.

3.1.13 Additional Monitoring and Considerations

3.1.13.1 Cytomegalovirus (CMV) Reactivation

CMV reactivation can occur in subjects treated with copanlisib and is manifested by positive CMV PCR without evidence of active CMV infection or organ involvement. CMV screening will be performed in all subjects before study enrollment. This will include CMV IgM and IgG status as well as baseline CMV PCR.

Subjects with a positive CMV PCR at screening will not be enrolled onto the study per exclusion criteria (Section **2.1.2.3**). All subjects will have CMV PCR drawn before each new cycle, and each surveillance visit until 6 months after therapy is complete (see Study Calendar, Section **0**). If a surveillance CMV PCR becomes positive during therapy, then they will be assessed for evidence of organ involvement. If no organ involvement, subjects can continue on study therapy at the discretion of the PI and will be managed according to local standards including use of anti-CMV medications such as valganciclovir. If subjects develop CMV infection associated with organ involvement, they will be treated with anti-CMV medications and removed from study therapy.

3.1.13.2 Hepatitis B Reactivation

Patients who test positive for either Hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) and not actuely infected are at varying risk for reactivation of Hepatitis B especially when combined with novel agents like copanlisib and/ or rituximab. Participants may be included in the study provided that they have HBV DNA levels below the World Health Organization's cutoff of 100 IU/mL prior to starting therapy. These patients will be treated with entecavir (or equivalent) during treatment and for 12 months after treatment has ended to prevent hepatitis B reactivation and should have HBV DNA levels obtained monthly for at least 12 months after the last cycle of therapy by means of real-time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

If the HBV DNA assay becomes positive during combination therapy, study treatment should be held, and the patient should be immediately referred to a gastroenterologist or hepatologist for management.

If the HBV DNA assay becomes positive and is ≤ 100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, study treatment must be held, and the patient should be immediately referred to a gastroenterologist or hepatologist for management.

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral medication, study treatment must be permanently discontinued

TREATMENT CONSIDERATIONS/EXCEPTIONS

3.1.14 Laboratory Criteria For Initiating A Cycle of Copanlisib with EPOCH-R

In order to initiate a subsequent cycle of treatment, subjects must meet minimum requirements for laboratory criteria as indicated below:

• Glucose	< 200 mg/dL (non-fasting)
• ANC	≥ 1,000/mm^3
• Platelets	≥ 75,000/mm^3
• ALT	<2.5 x ULN [a]
• AST	<2.5 x ULN [b]

a. < 5 x ULN in subjectss with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.
b. < 5 x ULN in subjects with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

POST-TREATMENT EVALUATIONS

When a subject completes all 6 cycles of treatment or discontinues early, all applicable activities scheduled for the End of Treatment Visit should be performed at the time of discontinuation (see Study Calendar- Section **0**). Any adverse events which are present at the time of discontinuation should be followed in accordance with the safety requirements outlined in Section **7**.

Regardless of a subject's disease status, follow-up must continue for at least 3 years after the last dose of study drug to meet the reporting requirements of the industry supporters (e.g., for purposes of reporting of secondary malignancies; see Section **0**).

All post-treatment visit(s) may be completed by remote visit with a member of the study team (e.g., if the subject is not able to return to the NIH CC). Remote visits will be conducted in compliance with NIH guidelines and FDA regulations. Required clinical labs/scans can be obtained by a local provider, with results sent for review and any suggested management by the study team. For clinical laboratory evaluations conducted with local providers, interlaboratory variability is not a concern as the lab tests are all routine; correlative samples are required only in follow-up visits that occur at NIH. A subject may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the investigator; otherwise, physical exams are not required at these time points. In the case of any visits with subjects' local providers, records will be obtained for the research records.

3.1.15 End of Treatment/ Disease Progression

Subjects will be evaluated at the end of study treatment (about 21 days following initiation of the last cycle of treatment [+/-7 days]), and post-treatment prior to (or at) disease progression.

3.1.16 Safety Follow-Up Visit

The safety follow-up visit should occur 30 days (±7 days) after the last dose of trial treatment, or before the initiation of a new anti-cancer treatment, whichever comes first. Required testing is as noted in the Study Calendars **0**. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. See section **6.1.1** for documentation of AEs after study treatment has ended.

3.1.17 Follow-Up Visits – Prior to Disease Progression

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 3 months for the first 2 years post-treatment and then every 6 months from years 2-5 post-treatment. The list of required assessments to be performed including disease evaluation; however, may include other necessary standard of care as clinically indicated at the discretion of the investigator (e.g., physical exam, CBC, chemistries). See the Study Calendar in Section **0**. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study.

3.1.18 Follow-Up Visits – Survival/Post-Disease Progression

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted at least every 3 months (+/-4 weeks) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (see Section **0**, Study Calendar).

STUDY CALENDAR

Procedure	**Screening**[1]	**Baseline**[2]	**Treatment**				**Response Assessment**	**End of Treatment**	**Follow-Up**		
			Before Cycles 2-6	C1D1	C1D5	Post Cycles 1-6	After Cycle 1, 3 and 6		Safety (Day 30)	Follow-Up (Prior to PD)	Survival (Post-PD/ Other Therapy)
Scheduling Window (Days):	-28 to -14		-3	±1			Last 7 days of the cycle	Treatment discon./PD[3]	+7	Every 3 or 6 months[4]	Every 3 months[5]
Confirmation of Diagnosis[17]	X										
Medical History	X	X	X	X							
Physical Exam[6]	X	X		X				X	X		
ECOG PS	X	X		X				X	X		
CBC with Differential	X	X	X	X				X	X		
Chemistry Panels[7]	X	X	X	X				X	X		
Hemoglobin A1C	X	X	X					X	X		
ECHO and EKG	X										
LDH		X	X					X	X		
Urinalysis	X	X	X					X	X		
Pregnancy Test (urine/serum; WOCBP) [8]	X	X	X								
HCV PCR and HIV Testing	X										
HBV serology	X										
HBV PCR	X		X[16]						X[16]	X[16]	X[16]
CMV PCR and CMV IgM and IgG[9]	X		X						X		
Lumbar Puncture[10]		X						X			
Bone Marrow Aspiration/Biopsy[11]	X							X			
Lymphocyte Phenotype (T, B, NK cell subsets)		X					X	X			
Peripheral Blood Flow Cytometry		X						X			
CT Scans[12]	X	X					X	X		X	
^{18}F-FDG-PET/CT Scan[13]	X	X					X	X			
MRI brain	X										
Symptoms/Adverse Events Assessment, Concomitant Medication Review	X	X	X	X				X	X		
Research Tissues (archival/fresh biopsy)[14]		X						X (PD)			

Procedure	Screening[1]	Baseline[2]	Treatment				Response Assessment	End of Treatment	Follow-Up		
			Before Cycles 2-6	C1D1	C1D5	Post Cycles 1-6	After Cycle 1, 3 and 6		Safety (Day 30)	Follow-Up (Prior to PD)	Survival (Post-PD/ Other Therapy)
Scheduling Window (Days):	-28 to -14		-3	±1			Last 7 days of the cycle	Treatment discon./PD[3]	+7	Every 3 or 6 months[4]	Every 3 months[5]
Research Saliva/Buccal (baseline only), Research Blood Samples[15]		X		X	X	X		X		X	
Survival Status			X								

NOTE: Additional assessments may be done as clinically indicated (e.g., necessary standard of care). See Section **0** for details on drug administration and Section **5** for details on correlative studies to be performed.

1 Screening evaluations should be performed within 28 days prior to confirmation of eligibility with the following exceptions: Confirmation of diagnosis (no time limit); HIV antibody, HBV, HCV and CMV PCR (within 3 months).

2 Any screening tests performed within the specified time frame for baseline do not need to be repeated. Baseline assessments to performed within 14 days prior to treatment with the following exceptions: bone marrow aspiration and biopsy (within 1 month); pregnancy test (within 7 days).

3 To be done at treatment discontinuation (+/- 2 weeks) or may coincide with the safety follow-up visit. If treatment is discontinued for a reason other than disease progression, assessments should be repeated at the time of progression. If subject to initiate new anti-cancer therapy assessments should occur before the first dose of the new therapy.

4 Follow-up to occur about every 3 months (+/- 2 weeks) for first 2 years post-treatment, every 6 months for years 2-5 (+/- 4 weeks), and then annually (+/- 6 weeks) at discretion of investigator until the study is stopped. Any other evaluations and tests should be performed as clinically indicated.

5 After disease progression or initiation of new anti-cancer therapy, contact for survival about every 3 months (+/- 4 weeks). See Section **3.1.18**.

6 Physical exams to include review of systems and changes since last visit, vitals, weight, and height (screening only).

7 Chemistry panels include: Acute care, Hepatic, and Mineral.

8 Pregnancy test for WOCBP required within 7 days of enrollment and again within 7 days of D1 in cycle 1 and within 7 days of D1 of each cycle .

9 CMV PCR will be performed at screening and at the start of every cycle. CMV IgM and IgG will be done at screening only. CMV PCR testing will be done during follow-up visits for the first 6 months after therapy.

10 Lumbar Puncture with cytology and flow cytometry if clinically indicated, at the end of treatment only if positive at baseline

11 Bone marrow aspiration with flow cytometry and biopsy (within 3 months prior to starting treatment) at the end of treatment only if positive at screening; repeat in follow-up to confirm response or progression.

12 CT scans (preferred) of chest, abdomen and pelvis at screening and baseline; may be adjusted to assess additional known sites of disease, as needed.

13 PET scans (i.e., whole body 18F-FDG PET/CT) to be performed after cycles 3 and 6 (last 7 days of each cycle).

14 If adequate archival tissue at baseline, fresh tumor biopsy is optional. Optional “on-treatment” tumor biopsies will be performed as described in Section **5**.

[15] Samples for correlative research blood and saliva (preferred)/buccal swab samples to be collected as indicated in Section **5**.

[16] Subjects on HBV prophylaxis (Section **2.1.2.6**) will have HBV DNA levels obtained monthly for at least 12 months after the last cycle of therapy per Section **3.1.13.2**.

[17] If adequate archival tissue is not available, a fresh biopsy for confirmation of diagnosis will be required.

COST AND COMPENSATION

3.1.19 Costs

NIH does not bill health insurance companies or subjects for any research or related clinical care that subjects receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, subjects may have to pay for these costs if they are not covered by their insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.1.20 Compensation

Subjects will not be compensated on this study.

3.1.21 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the subject/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy. Additional safety visits and follow-up will continue as per Section **0**.

3.1.22 Criteria for Removal from Protocol Therapy

- Completion of protocol therapy
- Confirmed clinical or radiographic disease progression
- Unacceptable toxicity as listed in Section **3.1.1** or those toxicities listed in Section **0** that requires treatment to be stopped.
- Intercurrent illness that prevents further administration of treatment
- Requirement for use of prohibited therapies as listed in Section **0**
- Pregnancy
- Subject's requests to be withdrawn from protocol therapy
- Noncompliance with trial treatment or procedure requirements that requires removal in the opinion of the PI
- Investigator's decision to withdraw the subject
- Study is cancelled for any reason

3.1.23 Off-Study Criteria

- Subject requests to be withdrawn from study
- Screen failure
- Subject is lost to follow-up
- Death
- Study is cancelled for any reason

3.1.24 Lost to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for two (2) scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The team will attempt to contact the subject and reschedule the missed visit within 7 business days and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

4 CONCOMITANT MEDICATIONS/MEASURES

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from trial therapy may be required.

ACCEPTABLE/PERMITTED MEDICATIONS

All treatments that the investigator considers necessary for a subject's welfare, including the use of growth factors support (e.g., filgastrim injections) may be administered at the discretion of the investigator in keeping with the community standards of medical care. Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all subjects in this trial.

All concomitant medication will be recorded including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

PROHIBITED MEDICATIONS

Subjects are prohibited from receiving the following therapies during treatment on this trial. Subjects who, in the assessment by the investigator, require the use of any of the following treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

- Other therapy for the disease under study not specified in this protocol, unless specifically noted as permitted
- Investigational agents other than copanlisib (chemotherapy or biologic agents)
- Radiation therapy
- Immunosuppressive therapy

- Anti-arrhythmic therapy (beta blockers or digoxin are permitted)
- Herbal preparations/medications. These include but are not limited to St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Subjects should stop using these herbal medications 7 days prior to first dose of study drug
- CYP3A4 inhibitors and inducers. Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 and strong inducers of CYP3A are not permitted. Moderate inhibitors should be used with caution.

  See below table of common medications. Please refer also to the following listing/ website: http://medicine.iupui.edu/CLINPHARM/DDIS

Category	Drug name
Strong CYP3A Inhibitors	Voriconazole, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin,
Moderate CYP3A Inhibitors	Grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges (citrus paradisi fruit juice)
Strong CYP3A Inducers	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)
CYP3A Substrates with NTI	Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine,

TUMOR LYSIS SYNDROME

Subjects will be monitored closely for laboratory evidence of tumor lysis syndrome (TLS) prior to and during treatment. TLS is a risk for subjects with DLBCL or BL who are treated with high cell-killing agents. Perform tumor burden assessment with CT scan and CBC with WBC differential, assess blood chemistry in all subjects and correct pre-existing chemistry abnormalities prior to initiation of treatment with elective admission for fluid hydration, correction of electrolyte abnormalities and closer monitoring is permitted at the discretion of the investigators and will not be considered an SAE if done in the first cycle (see Section **0**).

Subjects who show laboratory evidence of TLS as determined by elevated uric acid with hyperkalemia, hyperphosphatemia and/or elevated creatinine will be admitted to the hospital for appropriate management with intravenous fluids. Uric-acid lowering agents may include xanthine oxidase inhibitor allopurinol with or without rasburicase per the drug product package inserts.

OTHER CONSIDERATIONS (COPANLISIB IB)

4.1.1 Diet

Subjects must fast for at least 8 hours prior to the first dose of copanlisib. After the first dose, subjects should maintain a normal diet unless modifications are required to manage an AE such as elevated blood glucose, diarrhea, nausea or vomiting.

5 CORRELATIVE STUDIES FOR RESEARCH

BIOSPECIMEN COLLECTION

An important correlative focus of this study is to utilize multiplatform genomic analyses of tumor biopsies to identify biomarkers that predict response or resistance. To achieve this goal, tumor biopsies will be collected in all subjects prior to therapy and optional tumor biopsies will be performed at the time of disease progression. These optional biopsies will be studied by the Staudt lab using integrative analyses to further characterize mechanisms of both intrinsic and acquired resistance.

The molecular annotation will include a combination of gene-expression profiling, RNA sequencing, whole-exome sequencing, and identification of copy number abnormalities via array comparative genomic hybridization. Specific aims of these molecular correlates will be based on published literature regarding gene expression and molecular signatures that identify subsets of subjects who are considered high-risk for early treatment failure.

Lastly, we aim to identify mechanisms of therapeutic resistance through genomic analysis of circulating tumor DNA and biopsies taken before treatment and at time of clinical progression.

Sample	Collection Details	Time Points	Supervising Laboratory/ Investigator
Blood Samples			
ctDNA/cfDNA, Plasma banking	• 1 x 10 mL Streck/BCT	• Baseline • Post Cycles 1-6 • End of Treatment/ Disease Progression (PD) • Follow-up	Figg
PBMCs/ Immune subsets	• 1 x 8 mL CPT (sodium citrate)	• Baseline • Post-cycles 1-6 • PD • Follow-up	Figg
Pharmacokinetics (Copanlisib PK)	• 1 x 4mL lithium heparin (green) – *place sample on ice after collection* and • CSF: 0.5mL in cryovial*	• Cycle 1 Day 1: prior to Copanlisib Day 1: post-Copanlisib 1 hour (+/- 15 minutes) 2 hour (+/- 15 minutes) 10-12 hours (+/- 15 minutes) 24 hours (+/- 15 minutes) Day 5	Figg/ NEBA
Other Samples			
Archival	FFPE (block or slides); biopsy is required if archival is not adequate or unavailable	• Baseline only	NCI LP/ Staudt lab
Tumor Biopsy (optional)	Excision (single/multiple nodes) or core (4-6 passes); placed in formalin/FFPE and media per routine practice	• Screening/Baseline • PD	
Germline DNA	Blood, Buccal swab, or Saliva (preferred)	• Baseline	Figg

*Copanlisib PK samples (both CSF and blood) will be collected at all timepoints in subjects with an Ommaya reservoir. For subjects without an Ommaya reservoir all blood timepoints will be collected, but only a 1 hour post-Copanlisib CSF sample will be collected and will be optional.

NOTE:

- Tubes/media may be adjusted at the time of collection based upon materials available and/or to ensure the best viable samples are collected for planned routine and/or research analysis at the time of procedure.
- All blood/tubes – *with the exception of PK samples/tubes* – should remain at ambient temperature after collection and processed on the day of collection, do not place samples on ice.
- All correlative samples to be collected at the NIH; if a subject cannot return to the NIH for the specified visit in follow-up, then the correlative research sample is not required.

SAMPLE COLLECTION AND PROCESSING

5.1.1 Summary

The planned analyses described below may be done on leftover and/or shared sample portions from the respective laboratories, as needed. In addition to the prospectively collected samples below, leftover portions of samples sent for routine laboratory testing (e.g., plasma from CBC/hematologies) may also be retrieved for research tests prior to being discarded. The planned prospective analyses are identified below; laboratories may share resources or collaborate on analyses, if appropriate (e.g., isolation/analysis of DNA not prospectively planned by one lab may be incorporated if needed during the planned analyses).

Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

5.1.2 Blood Samples – Figg Lab

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov. The samples will be processed, barcoded, and stored in Dr. Figg's lab until requested by the investigator.

5.1.2.1 Peripheral Blood Mononuclear Cells (PBMCs)

- Collect blood in Cell Preparation Tubes with sodium citrate (e.g., blue/black speckled top); gently invert tubes 8-10 times immediately after collection.
- PBMCs will be isolated per routine laboratory techniques.

5.1.2.2 Circulating Tumor DNA (ctDNA) and plasma banking

- Collect blood in cell-free DNA (e.g., Streck BCT/collection tubes) gently invert the tubes 8-10 times immediately after collection.
- Plasma will be isolated and frozen at -80ºC until analysis (e.g., centrifuged at 1800 x g for 10 minutes at room temperature; plasma transferred/frozen in aliquots of 1.5-2 mL each).

5.1.2.3 Pharmacokinetics (PK) Sampling – Copanlisib blood samples

PK sampling will be performed in all subjects for copanlisib and its metabolite M-1 in the blood. CSF will be collected in all subjects with Ommaya reservoirs. For subjects without Ommaya, only a 1 hour post-copanlisib CSF sample will be collected and will be optional.

- Collect blood in specified tubes (e.g., 4 mL vacutainer tubes containing lithium-heparin)
- Immediately after collection, tubes must be gently inverted several times to mix with anticoagulant, and placed on ice until centrifugation. DO NOT SHAKE.
- As soon as possible after collection, plasma will be isolated (e.g., 2500 rpm for 15 minutes at 0-4°C).
- Transfer plasma equally to two 2-mL cryovials (e.g., 2mL screw cap polypropylene cryovial), and frozen upright at -60ºC to -80ºC within 60 minutes after the blood draw.
- Store at -80ºC until analysis

5.1.2.4 Pharmacokinetics (PK) Sampling – Copanlisib CSF samples

CSF will be collected at all timepoints in subjects with Ommaya reservoirs. For subjects without Ommaya, only a 1 hour post-copanlisib CSF sample will be collected and will be optional.

- Figg BPC lab staff member will add 10 µL of 10% Tween-80 to each cryotube (e.g., NUNC cryotube cat. # 366656 or 377224) prior to CSF collection. (**NOTE:** Do not use 10% Tween-80 solution past its expiration date.) Research team/designee will obtain cryotube described above from BPC prior to sample collection.
- Ommaya-certified personnel (RN, NP, PA, MD) or person performing lumbar puncture will collect 0.5 mL of CSF sample in the cryotube containing 10% Tween-80. The sample will be mixed thoroughly using a Vortex mixer and immediately placed in ice bath until samples can be processed.
- CSF samples will be centrifuged at 1,000 g for 10 minutes within one hour of collection in a clinical refrigerated centrifuge, maintained at approximately 4 °C, to yield supernatant cell free CSF from each 0.5 mL CSF sample.
- At least 300 µL of the cell free CSF supernatant will be transferred immediately into appropriately pre-labeled cryotubes (e.g., NUNC cryotube cat. # 366656 or 377224) with a new pipette tip for each sample.
- The cell-free CSF samples will be stored in an upright position, at –70°C or lower at the clinical site.
- The time between CSF collection and freezing the cell free CSF sample will be approximately 60 minutes.

5.1.3 Tissue Samples

5.1.3.1 Archival tissue

Archival block(s) or slides (i.e., at least 20 unstained slides, 5-microns) are preferred at baseline; these may also be required in follow-up in case of future routine procedures or in case additional tissue is needed even in the event of optional tumor biopsy.

5.1.3.2 Lymph node excision or core needle biopsy procedure (optional)

Lymph node excision or core needle biopsy will be performed per routine standard of care, by Surgery Consultants or Interventional Radiology, as appropriate. A procedure-specific consent form will be signed by the subject prior to the procedure. Every attempt will be made to perform excisional lymph node biopsies to obtain the best quality tissue for translational investigation. Consideration of alternative biopsy methods (e.g., core needle biopsy with ultrasound/CT guidance, as necessary) will only be made if follow-up excisional biopsy is not possible/safe or subject is unwilling to undergo repeat excisional lymph node biopsy.

In the event of core needle biopsy, these are obtained typically by using a 14-18G needle at the discretion of the provider performing the procedure. Conscious sedation may be used, if warranted, and the use and risks are acceptable to the subject.

Potential site(s) of biopsy include, but are not limited to: bone marrow lesions, bony lesions, extramedullary disease/masses, and lymph nodes. The type of procedure to be done and manner in which it will proceed (e.g., excision/core, single vs. multiple sites of biopsy) will be discussed with the subject prior to the biopsy procedure. The subject will be reminded that all sampling for research is voluntary.

5.1.3.3 Sample handling/processing

When performed, excisions or core biopsies will be placed in sterile collection/core cylinder tubes with appropriate media (e.g., formalin or sterile saline); gently invert/inspect tubes with media 8-10 times immediately after collection to ensure the core(s) is completed immersed in the media.

Tissue samples will be handled/processed as below prior to planned analyses, as appropriate:

- Any required routine review for histopathologic confirmation of diagnosis and/or grade will occur per standard of care (e.g., H&E, immunohistochemistry), if required.
- Formalin samples will be fixed and paraffin-embedded per routine techniques.

5.1.4 Other Samples

5.1.4.1 Germline DNA

Germline DNA will be collected by blood, buccal swab, and/or saliva samples (preferred). These will ideally be collected at baseline; however, may be collected at any point on study based on supplies. Standardized, commercial collection kits or tubes will be used (e.g., 1, 5-10 mL K_2EDTA tube for blood; Isohelix SK-1 for buccal swabs; Salviette/Oragene® for saliva). In the case of buccal swabs, two (2) samples may be collected in order to ensure adequate DNA collection.

The samples will be processed and DNA extracted/isolated per kit instructions and established techniques. These will also be handled by Dr. Figg's lab (see Section **5.1.2** for contact information).

BIOMARKER AND RESEARCH METHODS

The technology platforms that are able to interrogate genomic structure and function are constantly in flux; therefore, the exact nature of the methodologies that will be employed will be assessed at the time that the samples are collected and ready for analysis.

The following are technologies that are currently in use for each planned analysis:

5.1.5 Tumor Profiling

Immunohistochemical (IHC) analyses, including FISH for MYC, BCL2 or BCL6, will be done on every subject's baseline tumor biopsy. The routine IHC panel for diagnosis will be performed on tumor tissue samples, including but not necessarily limited to CD3, CD5, CD10, CD20, CD21, CD23, BCL2, BCL6, MUM1 and MIB-1.

5.1.6 DNA/RNA Sequencing

Genomic DNA and total RNA will be extracted from tumor samples using a Qiagen All-prep kit. For individual target genes that are recurrently mutated, classical Sanger sequencing will be performed on PCR amplicons, using primers surrounding the known sites of mutation. To broadly assess mutations, next generation sequencing (e.g., on an Illumina HiSeq 2000 platform) will be employed, using a paired end sequencing strategy of libraries constructed from tumor DNA. DNA will either be sequenced in its entirety from a whole genome library or will be first enriched for exonic sequences using the Agilent Sure Select system, aiming for 30X or 100X average coverage per base, respectively. The sequence fragments will be mapped back to the genome using the BWA algorithm. Of sequences overlapping a particular base pair in the genome, the percent mutant calls greater that 20% with a minimum of 25X coverage will be considered as an arbitrary threshold for single nucleotide variants (SNVs). SNVs that are not present in the matched normal sample will be considered candidate somatic mutations.

A related technology, RNA-Seq, utilizes RNA from the tumor specimen to create a cDNA library for high-throughput sequencing. RNA-seq will be performed using Illumina kits followed by high-throughput sequencing on an Illumina HighSeq 2000 machine. The cutoffs for coverage and percent mutant calls mentioned above will also be used to identify putative SNVs. RNA sequencing will also be used to read out digital gene expression across the genome as described.

Recent advances in genomic technologies enable GEP at the single cell level, a distinct advantage over conventional GEP which cannot always distinguish tumor vs non-tumor gene expression(50, 51). Single-cell approaches allow identification of the evolution of rare populations of resistant tumor cells, as well as identification of TME cells critical for the survival of the tumor. The Center for Cancer Research (CCR) has recently opened a single cell analysis core facility with expert staff headed by Dr. Michael Kelly within the CCR Genomics Core. This facility has the ability to take purified viably frozen cells banked from subject biopsies and prepare them, using well-validated 10X Genomics technology, for single-cell RNA sequencing. This core is directly integrated with the NCI Sequencing core facility to provide high-quality, deep-sequencing of the single cell RNA-SEQ samples, as well as 'first-pass' data processing and analysis. Data will then be transferred to lymphoma researchers and bio-informaticians in the Staudt lab for further analysis of gene expression patterns and cellular population dynamics.

5.1.7 DNA Copy Number Analysis

Array comparative genomic hybridization (e.g., on Agilent 240K or Affy SNP 6.0 microarrays) will be used to assess DNA copy number alterations as described, in tumor DNA to yield somatically acquired regions of copy number gain and loss.

5.1.8 Pharmacokinetics (PK)

Coded (linked) samples (Section **5.1.13**) will be sent to a contracted laboratory at the request of Bayer for analysis of copanlisib pharmacokinetics: NorthEast Bioanalytical Laboratories, LLC (NEBA) under the direction of Vipin Agarwal, Ph.D., MBA.

NEBA will run subject samples for PK analysis in batches; with the intent for reanalysis of samples due to out of calibration range concentration (i.e., secondary to large difference in parent and metabolite concentrations).

The laboratory contact information is as follows:

NorthEast Bioanalytical Laboratories LLC
925 Sherman Avenue
Hamden,CT 06514

5.1.9 Detecting Minimal Residual Disease (MRD)/ circulating tumor DNA (ctDNA)

5.1.9.1 Rationale for MRD assessment

Detecting Minimal Residual Disease (MRD) can be a powerful tool to monitor subjects' response to treatment and early detection of relapse. It is of research interest to determine if circulating tumor DNA before, during or after therapy is predictive of long-term disease-free survival. Adaptive Biotechnologies Corp will assess whether immune repertoire data (B-cell immunoglobulin receptor sequences or T-cell receptor sequences) from the Human Material can be used as biomarkers that correlate with disease-free survival. Adaptive Biotechnologies Corp will use a proprietary method, Immune Cell Receptor Sequencing (ICRS) platform, for amplifying and analyzing immune cell receptor sequences, allowing unprecedented sensitivity and specificity.

Data from experiments conducted by Adaptive Biotechnologies Corp using the human material will be provided to NCI and such data provided by Adaptive Biotechnologies Corp to NCI may be used by NCI for any purpose.

5.1.9.2 Samples to be sent to Adaptive Biotechnologies Corp

Bloods from the storage/future use samples collected from select subjects at the following time points may be sent, if available:

- Baseline
- Post C1-C6
- End of therapy
- Follow-up surveillance

5.1.9.3 Sample collection and processing

Portions of the other samples collected, including blood (serum, plasma and/or buffy coat), frozen or formalin fixed and paraffin embedded (FFPE) human tissue, and data from select subjects will be sent.

5.1.9.4 Shipping information

Only coded (linked) samples will be shared as described (see Section **5.1.13**) for process of coding, and sample request instructions. The samples and data will sent in batches to Adaptive Biotechnologies Corp at the address listed below.

Adaptive Biotechnologies Corp.
1551 Eastlake Ave E
Suite 200
Seattle WA 98102

5.1.10 Other Analyses

Other analyses include the following:

- Cell analysis and histological (e.g., H&E), immunohistochemical review and analysis per standard and established research techniques (e.g., FISH for BCL2, MYC, BCL6 translocation, and other IHC analyses in blood and tissue).
- cfDNA/ctDNA for liquid genotyping as a non-invasive dynamic monitoring of disease as well as monitoring for individual molecular aberrations that herald progression or disease transformation; specifically, amplification and sequencing of the VDJ segment of the immunoglobulin receptor is planned

5.1.11 Future Use

Any blood, tissue, or other products or portions leftover from other analyses will be stored for future research.

SAMPLE STORAGE, TRACKING AND DISPOSITION

5.1.12 General

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **0**.

If the subject withdraws consent his/her data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

5.1.13 Clinical Pharmacology Program (Figg Lab)

5.1.13.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) of the Clinical Pharmacology Program under the direction of Dr. Figg will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to subjects without Labmatrix access. The data recorded for each sample includes the subject ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Subject demographics associated with the clinical center subject number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.1.13.2 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezers at appropriate temperatures (e.g., -20ºC to -80ºC) according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Sample barcodes are linked to subject demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to subject information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.1.14 Hematopathology Section of Laboratory of Pathology (Tissue samples)

Archival and/or freshly collected and processed tumor tissue may be stored in the Hematopathology Section of Laboratory of Pathology until ready for planned and/or future research assays if the subject has agreed to allowing specimens to be used in future research

studies. IRB approval will be obtained before using any samples to conduct studies that are not described within this protocol. Samples will be stored under conditions appropriate to the type of sample and processing (e.g., ambient or frozen).

Tissue that is given to the technician will be assigned an accession number (HP#) in the HP Case Log book; sample tracking also takes place with a FileMaker Pro data base called HP Patient Information and Specimen Inventory. A subject background sheet may be filled out and filed with any accompanying paperwork, with final reports and any supplemental reports that follow added as completed.

5.1.15 Staudt Lab

5.1.15.1 Sample Data Collection

Subject samples, collected for research under this IRB approved protocol, may be archived in the Staudt laboratory. All data associated with archived clinical research samples is entered into the web-based NCI Labmatrix database, a centralized system with access controlled via centralized login. Access to this database for samples collected from this study is limited to Dr. Staudt and his research staff, each requiring individual login and password. All staff in the laboratory receive annually updated NIH/CITI or other training, as appropriate, and maintain standards of computer security.

The data recorded for each sample may include the subject ID, trial name/protocol number, date drawn/collected, treatment cycle/time point, sample source (e.g., peripheral blood, marrow, tissue, etc.) as well as box and freezer location. All received samples will be given a unique bar code number, which will be added to the sample NCI Labmatrix database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to subjects without authorized access to the NCI Labmatrix database.

5.1.15.2 Sample Storage

Samples are stored in freezers at -80°C (e.g., sera, plasma, tissue samples) or under liquid nitrogen (e.g., cells), according to established stability requirements. These freezers are located onsite under the direction of Dr. Staudt. Access to samples from this protocol for research purposes will be as outlined in this protocol or by permission of the Principal Investigator only.

SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.1.16 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ct) DNA. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.1.17 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **0**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.1.18 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

5.1.19 Genetic Counseling

Subjects will be contacted with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

DATA COLLECTION

6.1.1 Summary

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject subject.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first administration of study drug through 30 days post the last administration of study drug. After 30 days, only adverse events which are serious and related to the study intervention need to be recorded.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred,this will be reported expeditiously per requirements in section **7.1.1**.

6.1.2 Data Collection/Recording Exceptions

6.1.2.1 Abnormal Laboratory Values

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms

- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the subject's outcome.

DATA SHARING PLANS

6.1.3 Human Data Sharing Plan

What data will be shared?
I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in another public repository

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_X_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?
Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov, dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Approved outside collaborators under appropriate individual agreements.

_X_ Publication and/or public presentations.

When will the data be shared?
_X_ Before publication.

_X_ At the time of publication or shortly thereafter.

6.1.4 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

RESPONSE CRITERIA

The response categories being used to assess overall efficacy of combination therapy are based on the Revised Response Criteria for Malignant Lymphoma (52). Tumor response will be assessed by the investigator using the Lugano Classification Response Criteria for NHL (see **Appendix C**).

6.1.5 Complete Response (CR)

For CR determination, all the following criteria must be met:

1. Complete disappearance of all detectable evidence of disease and disease-related symptoms, if present before therapy
2. All lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in the greatest transverse diameter [GTD] for nodes >1.5 cm before therapy, regardless of the short axis). Previously involved nodes that were between 1.1 cm and 1.5 cm in the long axis and more than 1.0 cm in the short axis before treatment must have decreased to ≤1.0 cm in the short axis after treatment. All splenic and hepatic nodules and other extranodal disease must have disappeared.
3. FDG-PET scan must be negative (for the combined CT+PET assessment of CR). A posttreatment residual mass of any size is permitted as long as it is PET-negative. The Five-Point Scale (5-PS) Deauville criteria will be used to interpret PET scans with a score of 1-3 being considered PET negative and 4-5 considered PET positive (53) (Section **6.1.9**).
4. The spleen and/or liver, if enlarged before therapy on the basis of physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies.
5. If the bone marrow was involved before treatment, the infiltrate must have cleared on repeated bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If a sample is indeterminate by morphology, it should be negative by IHC (if bone marrow was involved before therapy and a radiological CR was achieved, but with no bone marrow assessment after treatment, the response should be classified as a PR).
6. No new sites of disease are detected during assessment.

6.1.6 Partial Response (PR)

For PR determination in subjects with measurable disease, all the following criteria must be met:

1. A ≥50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses.
2. No increase should be observed in the size of other nodes, liver, or spleen, meeting the criteria for PD.
3. Splenic and hepatic nodules must regress by ≥50% in the SPD or, for single nodules, in the GTD.
4. With the exception of splenic and hepatic nodules, other organs should not have any measurable disease.
5. Bone marrow assessment is not required for PR determination.
6. No new sites of disease should be observed.
7. At least 1 PET-positive site of disease (required for the CT+PET assessment of PR).

For PR determination in subjects with evaluable disease that is not measurable, all the following criteria must be met:

1. A ≥50% decrease in the SUVmax from baseline PET scan.
2. Bone marrow assessment is not required for PR determination.
3. No new sites of disease should be observed.
4. At least 1 PET-positive site of disease (required for the CT+PET assessment of PR).

6.1.7 Stable Disease (SD)

Stable disease (SD) is defined as:

1. A subject is considered to have stable disease when he or she fails to attain the criteria needed for a CR, PR, or MR but does not fulfill those for PD.
2. The PET should be positive at, at least 1 previously involved site of disease, with no new areas of lymphoma involvement on the posttreatment CT or PET (for the combined CT+PET assessment of stable disease).

6.1.8 Progressive Disease (PD) or Relapsed Disease

Progressive disease or relapsed disease (after CR) is defined as:

1. Appearance of any new nodal lesion ≥1.6 cm in greatest tumor dimension or ≥1.1 cm in short axis during or after the end of therapy, even if other lesions are decreasing in size.
2. Appearance of any new unequivocal extra-nodal lesion measuring >1.0 cm, not thought to be benign by the reviewer, even if other lesions are decreasing in size
3. At least a 50% increase from the nadir in the sum of the product of diameters of any previously involved nodes, or in a single involved node, or in the size of other lesions (e.g., splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of <1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
4. At least a 50% increase from the nadir in the longest diameter of any single previously identified node more than 1 cm in its short axis.
5. Cytology confirmation of DLBCL is required when there is an appearance on CT of a new lesion ≥1.5 cm in its long axis and is PET-negative.

6.1.9 The Five-Point Scale (5-PS) Deauville criteria

The five-point scale (5-PS) has been validated for use at interim staging and at the end of treatment and was adopted as the preferred reporting method at the First International Workshop on PET in Lymphoma in Deauville, France (i.e., Deauville criteria), and in several international trials.

The 5-PS scores the most intense uptake in a site of initial disease:

1. if present, as follows:no uptake or no residual uptake (when used at interim)
2. slight uptake, but below blood pool (mediastinum)
3. uptake above mediastinal, but below or equal to uptake in the liver
4. uptake slightly to moderately higher than liver
5. markedly increased uptake or any new lesion (on response evaluation)

6.1.10 Best Overall Response

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

6.1.11 Event-Free Survival

Event-free survival (EFS) is defined as the time from the date of study enrollment until time of disease relapse from CR, disease progression, initiation of subsequent systemic anti-lymphoma therapy for either PET-positive or biopsy-proven residual disease, or death, whichever occurs first.

Subjects who have not had any of these events will have their follow-up time censored at the date they are last known to be alive and event free.

6.1.12 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the date of study enrollment until time of disease relapse from CR, disease progression, or death, whichever occurs first. Subjects who have not had progression and are still alive will have their follow-up censored at the date they are last known to be alive without progression.

6.1.13 Overall Survival

Overall survival (OS) is defined as the time from the date of study enrollment until time of death from any cause. Subjects who remain alive will have their follow-up censored at the date they were last known to be alive.

TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each subject while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.1.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at

https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.1.2 IRB Requirments for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.1.3 Principal Investigator/Research Team

The clinical research team will meet approximately weekly when subjects are being actively treated on the trial to discuss each subject. Decisions about trial continuation will be made based on the efficacy data from prior Subjects at appropriate time points per the statistical plan.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.1.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each subject to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.1.4 Independent Monitoring Committee

Safety oversight for this study will include an Independent Safety Monitoring Committee consisting of the Principal Investigator and two qualified investigators who are not involved in the study and who are independent of the study team. The committee meetings will initially be contingent on patient accrual. A meeting will be scheduled with every 3 patients accrued during dose escalation and then every 6 patients during dose expansion. During these meetings, the committee will review all cumulative safety data and adverse events irrespective of the principal investigator's attribution of causality. Ad hoc meetings may be called at more frequent intervals at the request of the independent reviewers or based on the study participants' experience or the emergence of any safety signal. The study monitoring plan and study stopping rules may be amended as needed based on the accumulating safety and tolerability profile. The PI will be responsible for promptly alerting the independent reviewers of any suspected emerging safety signals. All Adverse Events, expected or unexpected, will be described in the routine safety monitoring reports. Unresolved differences regarding attribution of causality, event reporting, event management, or stopping criteria will be submitted for appropriate adjudication and reported promptly to the IRB.

8 SPONSOR PROTOCOL/ SAFETY REPORTING

DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a

medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **0**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section

REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **0**

All SAE reporting must include the elements described in section **0**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

WAIVER OF EXPEDITED REPORTING TO SPONSOR (CCR)

Death or hospitalization that is deemed to be due to disease progression, and not attributable to the intervention, will not be reported as an SAE. The event, and the assessment that it was caused by disease progression will be documented in the medical records. The causality assessment of hospitalization will be re-evaluated any time when new information is received. If the causality assessment changes from disease progression to related to the study intervention, SAE report will be sent to the Sponsor immediately in an expedited manner according to section **0**. If there is any uncertainty whether the intervention is a contributing factor to the event, the event should be reported as AE or SAE as appropriate.

If subjects considered high-risk for tumor lysis syndrome (TLS) are electively admitted to the hospital for the first cycle for close monitoring and supportive care to prevent TLS, then this will not be considered an SAE. The new onset of TLS that results in admission is considered an SAE.

The PI will submit a summary table of all grade 3-5 events, whether or not considered related to the product, every 6 months. The report shall include the number of participants treated in the timeframe, the number of events per AE term per grade which occurred in the 6-month timeframe and in total since the start of the study, attribution, and type/category of serious.

Reports will be submitted to the Center for Cancer Research (CCR) at OSROSafety@mail.nih.gov

The Sponsor might request case summaries for those events if, upon review, the Sponsor determines that an aggregate safety report is required (21CFR312.32(c)(1)(iv)).

SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.1.6 Maternal exposure

If a subject becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (**8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

Pregnancy should be reported using OSRO pregnancy reporting forms at the following location:

https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.1.7 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm for at least 3 months after the last dose of copanlisib and 12 months after the last dose of rituximab, whichever is later.

Pregnancy of the subject's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until at least 1 month after the last dose of copanlisib and 12 months after the last dose of rituximab, should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse

reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit

(SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the Recommended Phase II dose (RP2D) and Maximal tolerated dose (MTD) of copanlisib in combination with DA-EPOCH-R in subjects with Burkitt lymphoma (BL) and high grade B-cell lymphomas-double hit/triple hit (HGBCL-DH/TH) who have relapsed after or are refractory to chemo-immunotherapy	RP2D, MTD assessed during the first 21 days of treatment	Standard endpoint for phase I trial, see Section **3.1.1**
Secondary		
To assess the safety and tolerability of the combination of copanlisib and DA-EPOCH-R in subjects with BL and HGBCL-DH/TH relapsed after or refractory to chemo-immunotherapy	Dose level Adverse Events (AE) per CTCAE v5.0, by type and grade of toxicity, from first dose through end of treatment, see Section also **6.1.1**	Standard for phase I trials, collecting information on all major organ function and observed toxicity, if any, to determine prominent toxicity to advise safety and tolerability

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To determine the complete response rate, based on Lugano Criteria of the combination of copanlisib and DA-EPOCH-R in subjects with BL and HGBCL-DH/TH relapsed after or refractory to chemo-immunotherapy	Complete response (CR) rate, time measurement criteria are met for CR until the first date that progressive disease is objectively documented or death, assessed every 3-6 months	Standard endpoints for cancer clinical trials, CR is the endpoint chosen because with these diseases, PR is not relevant as all subjects will relapse. Regimens will not be moved forward unless they can achieve a CR.
To assess progression free survival (PFS), event-free survival (EFS) and overall survival (OS) of subjects treated with the combination of copanlisib and DA-EPOCH-R in subjects with BL and HGBCL-DH/TH relapsed after or refractory to chemo-immunotherapy	- Overall survival (OS)- time from the date of study enrollment until death from any cause, assessed every 3-6 months - Event free survival (EFS)- time from the date of study enrollment until time of disease relapse from CR, disease progression, initiation of subsequent systemic anti-lymphoma therapy for either PET-positive or biopsy-proven residual disease, or death, whichever occurs first, assessed every 3-6 months - Progression free survival (PFS) - time from date of study enrollment until time of disease relapse, disease progression, or death, whichever occurs first, assessed every 3-6 months	Standard endpoints for cancer clinical trials. Success of regimens will be determined by these endpoints.
Tertiary/Exploratory		
To explore the molecular correlates of resistance to copanlisib with DA-EPOCH-R	Each of these will be evaluated using descriptive methods and reported as exploratory results. If any statistical tests are performed in these analyses, the results will be presented without adjustment for multiple comparisons but reported in the context of the number of tests performed. See Section for **0** collection timepoints.	Exploratory analysis
To determine role of circulating tumor DNA to monitor response to therapy		
To determine the ability of circulating tumor DNA to predict disease relapse		
To explore the pharmacokinetics of copanlisib in plasma and cerebrospinal fluid (CSF) samples		

STATISTICAL HYPOTHESIS

- Primary Endpoint
    - Maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of copanlisib in combination with DA-EPOCH-R

- Secondary Endpoints
  - PFS, EFS, and OS
  - Overall safety profile of regimen
  - Rate of complete response

SAMPLE SIZE DETERMINATION

The primary objectives of this trial are to determine the safety and MTD or RP2D of the combination of dose-adjusted EPOCH-R and copanlisib and to obtain preliminary estimates of efficacy in subjects with relapsed Burkitt lymphoma or diffuse large B-cell lymphoma.

The original study design accrued 5 subjects to dose escalation (Arm 1) before it was closed after 2 subjects had DLTs related to unacceptable hematologic toxicity. After a review of the full safety profile, the study was amended with new eligibility criteria and a modified dosing schedule. Arm 1 was closed to further accrual and the dose escalation phase was resumed with accrual into Arm 2.

The trial will begin with a new 3 dose-level 3+3 design escalating copanlisib starting at 30 mg along with DA-EPOCH-R. With 3 dose levels being explored, the trial may require up to 18 additional subjects to complete the dose escalation portion. The number of subjects with toxicity at each dose level will be reported, along with tables of grade and type of toxicity.

As a stopping rule for safety, if during the modified dose escalation or expansion cohort any grade 5 adverse events occur that are possibly related to study treatment or 3 or more subjects have immune-mediated adverse events that necessitate stopping of copanlisib, then no more subjects will be enrolled. If at any point in the study (dose escalation or dose expansion), more than 20% of subjects need to stop the EPOCH-R chemotherapy backbone due to hematologic or non-hematologic toxicity, then further enrollment will be stopped. These stopping rules apply to the entirety of study treatment and not just during the DLT window.

At the MTD or RP2D level with 6 subjects evaluated during the dose escalation portion of study, an additional expansion cohort of 10 subjects with either Burkitt lymphoma or DLBCL will be enrolled in order to obtain more safety data as well as to obtain preliminary efficacy data, focusing primarily on the rate of complete response (CR). The 16 subjects treated in a homogeneous fashion at the MTD or RP2D will be evaluated primarily for CR rate using all subjects combined and may also be reported in an exploratory fashion by disease type (Burkitt vs. DLBCL). The fraction of subjects with a CR will be reported overall as well as by disease type, including 95% confidence intervals. If results are promising, more definitive evaluations of efficacy would be planned. PFS, EFS, and OS will be reported as a secondary evaluation, based on all subjects in the study as well as focusing on the 16 subjects treated in a homogeneous fashion.

As an additional stopping rule for safety, if at any time after 3 subjects have enrolled in the expansion cohort, ≥1/3 subjects cumulatively treated in the expansion are identified as having a DLT, no further subjects will enroll. It is expected that 10-12 subjects per year may enroll on this study. With a maximum of 5+18+10=33 evaluable subjects, up to 3 years may be required to accrue up to 39 subjects, including for a small number of inevaluable subjects or screen failures. The increase in accrual is to account for the five subjects enrolled to the now closed Cohort 1 Arm 1 treated with the original drug dose regimen.

POPULATIONS FOR ANALYSES

10.1.1 Evaluable for Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with copanlisib.

10.1.2 Evaluable for Objective Response

Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (**NOTE**: Subjects who exhibit objective disease progression at any point after receiving at least 1 cycle of therapy will also be considered evaluable.)

10.1.3 Evaluable Non-Target Disease Response

Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

STATISTICAL ANALYSES

10.1.4 General Approach

Toxicity and safety data will be reported descriptively. The response rate will be determined and reported along with a 95% confidence interval. Other time-to-event outcomes will be reported using Kaplan-Meier curves.

10.1.5 Analysis of the Primary Endpoint

The number of subjects with toxicity at each dose level will be reported, along with tables of grade and type of toxicity.

10.1.6 Analysis of the Secondary Endpoints

Among the subjects treated at the MTD or RP2D, the complete response (CR) rate will be determined and reported along with a two-sided 95% confidence interval. Based on all subjects enrolled in the study as well as focusing on the 16 subjects treated in a homogeneous fashion, progression-free survival (PFS), event-free survival (EFS)and overall survival (OS) will be estimated using the Kaplan-Meier method for each. In addition to providing the curves for each endpoint, the median and a 95% confidence interval for the median will be reported. Adverse event data will be compiled and tabulated using descriptive statistics. The assessment of OS is estimated to end at 5 years after completion of treatment of the last subject.

10.1.7 Safety Analyses

The type, grade and frequency of toxicities will be reported.

As a stopping rule for safety, if at any time after 3 subjects have enrolled in the expansion cohort, ≥1/3 subjects cumulatively treated in the expansion are identified as having a DLT, no further subjects will enroll.

If during the modified dose escalation or expansion cohort any grade 5 adverse events occur that are possibly related to study treatment or 3 or more subjects have immune-mediated adverse events that necessitate stopping of copanlisib, then no more subjects will be enrolled.

If at any point in the study (dose escalation or dose expansion), more than 20% of subjects need to stop the EPOCH-R chemotherapy backbone due to hematologic or non-hematologic toxicity, then further enrollment will be stopped.

These stopping rules apply to the entirety of study treatment and not just during the DLT window.

10.1.8 Baseline Descriptive Statistics

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and CIs for discrete variables) will be used to summarize data as appropriate.

10.1.9 Planned Interim Analyses

None.

10.1.10Sub-Group Analyses

Analyses by disease type may be performed depending on the number of subjects available for inclusion in analyses.

10.1.11Tabulation of Individual Subject Data

None.

10.1.12Exploratory Objectives and Analyses

- To explore the molecular correlates of resistance to copanlisib with DA-EPOCH-R
- To determine role of circulating tumor DNA to monitor response to therapy
- To determine the ability of circulating tumor DNA to predict disease relapse

In addition, the CR rate may also be reported in an exploratory fashion by disease type (Burkitt vs. Large Cell). Moleculare correlates of resistance to copanlisib with DA-EPOCH-R will be reported descriptively. ctDNA studies are also exploratory and overall trends in serial measurements may support a response (or lack of response) signal to treatment and could be correlated with response and PFS as a surrogate marker of disease burden.

11 COLLABORATIVE AGREEMENTS

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT *(*CRADA)

A Cooperative Research and Development Agreement *(*CRADA) between the National Cancer Institute and Bayer Pharmaceuticals was executed prior to initiation of the trial (#03390).

12 HUMAN SUBJECTS PROTECTIONS

RATIONALE FOR SUBJECT SELECTION

All subjects from both sexes and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in the protocol. Subjects with HIV infection are included. Pregnant and nursing mothers are excluded because of the potential teratogenic effects of therapy.

PARTICIPATION OF CHILDREN

Children under the age of 18 will not be eligible for participation on this protocol because the response to treatments differs significantly between pediatric and adult BL and DLBCL subjects. Therefore, the inclusion of younger subjects will not provide generalizable information that would justify their inclusion on this study.

RISK/BENEFIT ASSESSMENT

12.1.1 Known Potential Risks

12.1.1.1 Risks from Study Drugs

The most common adverse reactions (≥10%) attributable to copanlisib observed in clinical trials were hyperglycemia, hypertension, diarrhea, decreased general strength and energy, neutropenia, nausea, lower respiratory tract infections and thrombocytopenia. The potential toxicity of copanlisib is reasonable in relation to the potential benefit to this group of subjects who have few treatment options.

The most common side effects of DA-EPOCH-R chemotherapy include: infection, bruising, fatigue, anemia, constipation, nausea/vomiting, constipation, tingling of fingers and toes, hair loss, fingernail discoloration, bony pain and infusion reactions.

These established risks are not anticipated to be significantly higher with the addition of copanlisib with DA-EPOCH-R in this study; however, the grades and frequencies of toxicities will be closely monitored and reported.

12.1.1.2 Blood Collection

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.1.1.3 Biopsy Collection

The risks of the biopsies include pain, bleeding and infection at the biopsy site. These biopsies may be performed with CT guidance.

12.1.1.4 Conscious Sedation

The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.1.1.5 ECG

Side effects of ECG are skin irritation where ECG electrodes are placed.

12.1.1.6 Echocardiogram

Side effects of an echocardiogram are discomfort from the transducer being firmly placed against the chest.

12.1.1.7 Bone Marrow Biopsy

Bone marrow biopsy is minimally invasive and is typically a very safe procedure. Usually the hipbone is numbed with anesthesia. Using a needle, the solid and liquid portion of bone marrow is taken out. This procedure causes some pain. Very rarely, infection or bleeding may occur at the needle site.

12.1.1.8 Lumbar Puncture

Risks of lumbar puncture include headache, dizziness, infection, back discomfort, minor radicular numbess and brainstem herniation

12.1.1.9 Imaging

In addition to the radiation risks discussed below, scans may include the risks of an allergic reaction to the contrast. Subjects might experience hives, itching, headache, difficulty breathing,

increased heartrate and swelling. Subjects undergoing gadolinium enhanced MRIs may also be at risk for kidney damage.

12.1.1.10 Radiation

The study will involve radiation from the following sources:

- Up to 7 CT (chest abdomen pelvis) scans per year for disease assessment
- Up to 5 FDG-PET scans per year for disease assessment
- Up to 2 CT-guided biopsies

Subjects in this study may be exposed to approximately 2.3 rem during screening and 13 rem during the study for a total of 15.3 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 1.5 out of 100 (1.5%) and of getting a fatal cancer is 0.8 out of 100 (0.8%).

12.1.1.11 Non-Physical Risks of Genetic Research

Risk of receiving unwanted information, anxiety and stress at the information, and breach of confidentiality.

12.1.1.12 Other Procedures

There are no physical risks associated with other procedures (e.g., urine or saliva collection, cheek/ buccal swabs).

12.1.2 Known Potential Benefits

Subjects may obtain direct benefit from treatment with copanlisib in combination with DA-EPOCH-R. See Section **1.1.8** and **1.1.9**.

CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the subject as applicable for review prior to consenting. A designated study investigator* will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the subject/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the subject will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at

https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

*****The informed consent process will involve the use of two consent forms, one labeled "Screening" (for all screening procedures) and another labeled "Standard" (for all study treatment/procedures). The consent for treatment must be obtained by a designated, appropriately licensed study investigator (e.g., MD, NP, PA, DO). Any study investigators not falling into this category (e.g., RNs) who are designated as able to obtain consent may do so for screening procedures only.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, funding agencies, the Investigational New Drug (IND) sponsor and regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NIH.

To further protect the privacy of study subjects, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

14 PHARMACEUTICAL INFORMATION

COPANLISIB (BAY 80-6946, ALIQOPA®) (IND #141280)

Refer to the FDA approved package insert for complete product information.

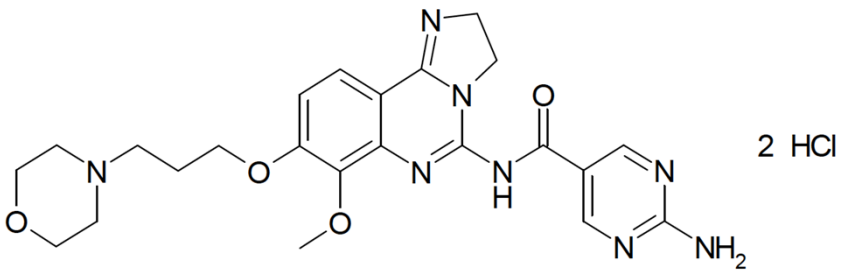
14.1.1 Source, Acquisition and Accountability

Copanlisib (commercial/marketed supplies) will be provided by Bayer Pharmaceuticals for use by subjects in this clinical trial.

14.1.2 Chemical formula and molecular structure

BAY 80-6946 is the active ingredient (free base) of BAY 84-1236, the dihydrochloride salt, which is used to prepare the freeze dried medicinal product. BAY 84-1236 is isolated either in its pseudopolymorphic form hydrate I (containing 11-17% water) or dried to a water content below 10%. Copanlisib has been assigned as the International Nonproprietary Name (INN) for BAY 80-6946.

Chemical Name (IUPAC):	2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride
BAY number:	BAY 80-6946 (free base); BAY 84-1236 (dihydrochloride salt)
Chemical formula:	C23H28N8O4 2HCl
Molecular mass:	553.45 g/mol
Chemical structure:	



14.1.3 Mechanism of copanlisib

Copanlisib is a small molecule pan-class 1 PI3K inhibitor with predominant activity against PI3Kα and PI3Kδ isoforms that first demonstrated anti-tumor activity in pre-clinical models characterized by activating genetic aberrations of the PI3K pathway. Copanlisib exhibits potent kinase inhibitory effect on all four isoforms with biochemical IC50 values of 0.5 nM, 0.7 nM, 3.7 nM and 6.4 nM for PI3Kα, PI3Kδ, PI3Kβ and PI3Kγ, respectively. Copanlisib also potently regulates nuclear localization of the forkhead family members resulting in the induction of transcriptional programs that lead to rapid cell death by apoptosis.

14.1.4 Toxicity

The safety data reflect exposure to copanlisib in 168 adults with follicular lymphoma and other hematologic malignancies treated with copanlisib 60 mg or 0.8 mg/kg equivalent in clinical trials. The median duration of treatment was 22 weeks (range 1 to 206 weeks).

Serious adverse reactions were reported in 44 (26%) subjects. The most frequent serious adverse reactions that occurred were pneumonia (8%), pneumonitis (5%) and hyperglycemia (5%). The most common adverse reactions (≥20%) were hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, and thrombocytopenia. Adverse reactions resulted in dose reduction in 36 (21%) and discontinuation in 27 (16%) subjects. The most common reasons for dose reduction were hyperglycemia (7%), neutropenia (5%), and hypertension (5%). The most common reasons for drug discontinuation were pneumonitis (2%) and hyperglycemia (2%).

The tables provide the serious adverse reactions occurring in subjects receiving copanlisib. Monotherapy (**Table 9**), and the treatment-emergent laboratory abnormalities in ≥10% of patients and ≥4% of Grade ≥3 treated with copanlisib and rituximab (**Table 10**).

Table 9: Serious Adverse Reactions From Multiple Clinical Trials

ADVERSE REACTIONS	Copanlisib N=877		
	All SAR N (%)	Life threatening	Fatal
Metabolism and nutrition disorders			
Hyperglycemia	39 (4.4%)	NA	NA
Blood and lymphatic system disorders			
Febrile neutropenia	13 (1.5%)	NA	NA
Neutropenia (including febrile neutropenia)	14 (1.6%)	NA	NA
Thrombocytopenia	2 (0.2%)	NA	NA
General disorders and administration site conditions			
Fatigue	2 (0.2%)	NA	NA
Gastrointestinal disorders			
Diarrhea	11 (1.3%)	NA	NA
Colitis	5 (0.6%)	NA	NA
Pancreatitis	2 (0.2%)	NA	NA
Vomiting	2 (0.2%)	NA	NA
Vascular disorders			
Hypertension (includes secondary hypertension)	8 (0.9%)	NA	NA
Infection			
Pneumonia	41 (4.7%)	NA	NA
Pneumocytis jirovecii	14 (1.6%)	NA	NA
Lower respiratory infection	5 (0.6%)	NA	NA
Bronchitis	4 (0.5%)	NA	NA
Pneumonia, bacterial	4 (0.5%)	NA	NA
Sepsis	4 (0.5%)	NA	NA
Herpes Zoster	3 (0.3%)	NA	NA
Pneumococcal pneumonia	2 (0.2%)	NA	NA
Pneumonia, viral	2 (0.2%)	NA	NA
Septic shock	2 (0.2%)	NA	NA
Metabolism and nutrition disorders			
Hyperglycemia	39 (4.4%)	NA	NA
Hyponatremia	2 (0.2%)	NA	NA
Pneumonitis	33 (3.8%)	NA	NA
Interstitial lung disease	11 (1.3%)	NA	NA
Skin and Subcutaneous Tissue Disorders			
Dermatitis exfoliative generalised	4 (0.5%)	NA	NA

Table 10: Treatment-emergent Laboratory Abnormalities in ≥10% of Patients and ≥4% of Grade ≥3 Treated with Copanlisib and Rituximab

Laboratory Parameter	Copanlisib with Rituximab N=307		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematology abnormalities			
Decreased hemoglobin	209 (68%)	15 (5%)	0
Lymphocyte count decreased	231 (76%)	73 (24%)	13 (4%)
Platelet count decreased	182 (60%)	11 (4%)	3 (1%)
Neutrophil count decreased	226 (74%)	58 (19%)	64 (21%)
Serum chemistry abnormalities			
Hyperglycemia	296 (96%)	193 (63%)	14 (5%)
Hypophosphatemia	127 (42%)	24 (8%)	4 (1%)
Hyponatremia	89 (29%)	16 (5%)	1 (0.1%)
Serum lipase increase	97 (32%)	17 (6%)	3 (1%)

14.1.5 Formulation and Preparation

The following excipients are used to manufacture the medicinal product: mannitol, NaOH, citric acid (except for the 20 mg formulation) and water for injection. The medicinal product is a freeze-dried product containing either 20 mg of copanlisib (equivalent to 23.04 mg BAY 84-1236) or 60 mg of copanlisib (equivalent to 69.12 mg BAY 84-1236) or 80 mg of copanlisib (equivalent to 92.16 mg BAY 84-1236) in a 6 mL injection vial. The IV solution is obtained after reconstitution of the lyophilisate with saline solution. The resulting solution contains the active substance in concentrations as outlined below:

Table 3–1: Reconstitution volumes and resulting copanlisib (BAY 80-6946) concentrations of the 20, 60, and 80 mg formulations

Formulation	Reconstitution volume [mL]	Resulting concentration of BAY 80-6946 [mg/mL]
20 mg	2	10
60 mg	4.4	15
80 mg	4	20

For example, for the 60 mg formulation: reconstitute copanlisib with 4.4 mL of sterile 0.9% NaCl solution leading to a concentration of 15 mg/mL, as follows:

- Withdraw 4.4 mL of sterile 0.9% NaCl solution by using a 5 mL sterile syringe with needle.
- Inject the measured volume through the disinfected stopper surface into the vial of copanlisib.
- Dissolve the lyophilized solid by gently shaking the injection vial for 30 seconds.
- Allow to stand for one minute to let bubbles rise to the surface.
- Check if any undissolved substance is still seen. If yes, repeat the gentle shaking and settling procedure.
- Inspect visually for discoloration and particulate matter. After reconstitution, the solution should be colorless to slightly yellowish

- Once the solution is free of visible particles, withdraw the reconstituted solution for further dilution.
    - The reconstituted solution is to be diluted with isotonic sodium chloride (NaCl) solution without falling below a concentration of 0.3 mg/mL copanlisib.

Further dilute the reconstituted solution in 100 mL sterile 0.9% NaCl solution for injection. With a sterile syringe, withdraw the required amount of the reconstituted solution for the desired dosage:

60 mg: Withdraw 4 mL of the reconstituted solution with a sterile syringe.
45 mg: Withdraw 3 mL of the reconstituted solution with a sterile syringe.
30 mg: Withdraw 2 mL of the reconstituted solution with a sterile syringe.

Inject the contents of the syringe into the subject infusion bag of 100 mL sterile 0.9% NaCl solution. Mix the dose well by inverting.

14.1.6 Stability and Storage

The drug product has to be stored between +2°C and +8°C and should not be transported above +30°C. Supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial supplies must be recorded by an authorized person at the trial site. Supplies may not be used for any purpose other than that stated in the protocol.

The diluted solution is physically and chemically stable for 24 hours at room temperature, provided it is not exposed to direct sunlight. However, for microbiologic consideration, diluted solution should be stored between +2°C and +8°C if not administered immediately.

Use reconstituted and diluted copanlisib immediately or store the reconstituted solution in the vial or diluted solution in the infusion bag at 2°C to 8°C (36°F to 46°F) for up to 24 hours before use. Allow the product to adapt to room temperature before use following refrigeration. Avoid exposure of the diluted solution to direct sunlight.

14.1.7 Administration procedures

Copanlisib is administered in a normal saline solution, intravenously, over 1 hour. Administer copanlisib as a single agent, following reconstitution and dilution. Mix only with 0.9% sodium chloride (NaCl) solution. Do not mix or inject copanlisib with other drugs or other diluents. No intravenous glucose preparations should be administered on the days of infusion.

RITUXIMAB

14.1.8 Source, Acquisition and Accountability

Commercial supplies of rituximab will be purchased by the NIH Clinical Center. Refer to the FDA approved package insert for complete product information including toxicity, formulation and preparation, stability and storage and incompatibilities.

14.1.9 Administration procedures

A peripheral or central intravenous line will be established. During rituximab infusion, a subject's vital signs (blood pressure, pulse, respiration, temperature) should be monitored according to the standard of care. Medications readily available for the emergency management of anaphylactoid reactions should include: epinephrine (1:1000, 1 mg/mL) for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment.

Prophylaxis against hypersensitivity and infusion-related reactions associated with rituximab will include acetaminophen 650 mg and diphenhydramine hydrochloride 50-100 mg administered 30-60 minutes prior to starting rituximab.

Rituximab infusions will be administered to subjects primarily in an outpatient clinic setting.

- **First dose**:

  The initial dose rate at the time of the first rituximab infusion should be 50mg/hour (25 mL/hr) for the first 30 minutes. If no toxicity is seen, the dose rate may be escalated gradually in 50 mg/hour (25 mL/h) increments at 30 minute intervals to a maximum of 400 mg/hour (maximum rate = 200 mL/h).

- **Second and Subsequent Doses (select the appropriate administration timing):**

  - ***90-minute Administration***

    If the first dose of rituximab is well tolerated, subsequent doses may be administered over 90 minutes with 20% of the total dose given in the first 30 minutes, and remaining 80% of the total dose administered over the subsequent 60 minutes; e.g.:

Two-Step Rate Escalation	Volume to administer (X mL)
1st portion (0 – 30 minutes)	$\frac{\text{Total Dose (mg)}}{2} \times 0.2 = \text{X mL (over 30 min)}$
2nd portion (30 – 90 minutes)	$\frac{\text{Total Dose (mg)}}{2} \times 0.8 = \text{X mL (over 60 min)}$

    Special Note: The 90-minute infusion scheme is not recommended for subjects with clinically significant cardiovascular disease or high circulating lymphocyte counts (≥5000/mcL).

  - ***Standard Administration for Second & Subsequent Infusions***

    Subjects who tolerate initial treatment without experiencing infusion-related adverse effects but for whom the 90-minute infusion scheme during subsequent treatments is considered inappropriate, may receive subsequent rituximab doses at the Standard Rate for Subsequent Infusions, which is as follows:

    Begin at an initial rate of 100 mg/hour (50 mL/h) for 30 minutes. If administration is well tolerated, the administration rate may be escalated gradually in 100-mg/hour (50-mL/h) increments at 30-minute intervals to a maximum rate of 400 mg/hour (maximum rate = 200 mL/h).

CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

DOXORUBICIN

14.1.10Source, Acquisition and Accountability

Doxorubicin is commercially available and will be supplied by the NIH Clinical Center Pharmacy Department. Refer to the FDA approved package insert for complete product information including toxicity, formulation and preparation, stability and storage and incompatibilities.

14.1.11Administration Procedures

For Dose-adjusted EPOCH-R, refer to Section **0** for administration procedures.

PREDNISONE

14.1.12Source, Acquisition and Accountability

Prednisone is commercially available and will be supplied to the subjects enrolled on the study by the NIH Clinical Center Pharmacy Department. Refer to the FDA approved package insert for complete product information including toxicity, formulation and preparation, stability and storage and incompatibilities.

14.1.13Administration Procedures

For Dose-adjusted EPOCH-R, prednisone will be administered twice daily by mouth on Days 1-5.

VINCRISTINE

14.1.14Source, Acquisition and Accountability

Vincristine is commercially available and will be supplied by the NIH Clinical Center Pharmacy Department. Refer to the FDA approved package insert for complete product information including toxicity, formulation and preparation, stability and storage and incompatibilities.

14.1.15Administration procedures

For Dose-adjusted EPOCH-R refer to Section **0** for administration procedures.

CYCLOPHOSPHAMIDE

14.1.16Source, Acquisition and Accountability

Cyclophosphamide is commercially available and will be supplied by the NIH Clinical Center Pharmacy Department. Refer to the FDA approved package insert for complete product information including toxicity, formulation and preparation, stability and storage and incompatibilities.

14.1.17Administration procedures

Cyclophosphamide will be diluted in D5W or 0.9% NaCl and administered as an intravenous infusion over 30 minutes. Subjects will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration. All subjects should receive 1000 mL 0.9%NaCl @ 300 – 500 mL/hr with 500 mL given before starting cyclophosphamide administration and 500 mL given after completion of the cyclophosphamide administration.

ETOPOSIDE

14.1.18Source, Acquisition and Accountability

Etoposide is commercially available and will be supplied by the NIH Clinical Center Pharmacy Department. Refer to the FDA approved package insert for complete product information including toxicity, formulation and preparation, stability and storage and incompatibilities.

14.1.19Administration procedures

Refer to Section **0** for administration procedures for Vincristine/Doxorubicin/Etoposide Admixture for Dose-adjusted EPOCH-R regimen.

VINCRISTINE/DOXORUBICIN/ETOPOSIDE ADMIXTURE

14.1.20Formulation and preparation

For Dose-adjusted EPOCH-R, vincristine, doxorubicin, and etoposide comprising a daily dose (a 24-hour supply) will be diluted in 0.9%NS. Product containers will be replaced every 24 hours to complete the planned duration of infusional treatment. Product volumes will be determined by the amount of etoposide present in a 24-hour supply of medication. For daily etoposide doses <130 mg, admixtures will be diluted in approximately 500 mL 0.9%NS.

14.1.21Stability and Storage

Stability studies conducted by the Pharmaceutical Development Service, Pharmacy Department, NIH Clinical Center, have demonstrated that admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, USP at concentrations, respectively, of 1, 25 and 125 mcg/mL; 1.4, 35 and 175 mcg/mL; 2, 50 and 250 mcg/mL; and 2.8, 70 and 350 mcg/mL are stable for at least 36 hours at room temperature when protected from light. Also, admixtures containing vincristine, doxorubicin and etoposide concentrations of 1.6, 40 and 200 mcg/mL are stable for at least 30 hours at 32ºC.

14.1.22Administration procedures

Vincristine + doxorubicin + etoposide admixtures will be administered by continuous IV infusion over 96 hours with a suitable rate controller pump via a central venous access device.

15 LIST OF ABBREVIATIONS

ABC	Activated B-cells
AE	Adverse Event/Adverse Experience
ANC	absolute neutrophil count
BCL-2	B-cell lymphoma 2
BCL-6	B-cell lymphoma 6
BL	Burkitt Lymphoma
BM	Bone marrow
CFR	Code of Federal Regulations
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COO	Cell of origin
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DA	Dose-adjusted
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group – performance status
EFS	Event-free survival
EKG	Electrocardiogram
EPOCH-R	Etoposide phosphate, Prednisone, Vincristine sulfate (Oncovin), Cyclophosphamide, Doxorubicin hydrochloride (Hydroxydaunorubicin)-Rituximab, combination chemotherapy regimen
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FWA	Federal Wide Assurance
GCB	Germinal center B cell
GCP	Good Clinical Practice

GEP	Gene-expression profiling
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGBCL-DH/TH	High grade B-cell lymphomas- double hit/triple hit
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHC	Immunohistochemical
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MDRD	Modification of Diet in Renal Disease
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximal tolerated dose
N	Number (typically refers to subjects)
NDA	New Drug Application
NHL	Non-Hodgkin lymphoma
NIP	Non-infectious pneumonitis
NIH	National Institutes of Health
NOS	Not otherwise specified
OHSR	Office for Human Subjects Research
OS	Overall survival
PCR	Polymerase chain reaction
PET	Positron Emission Tomography
PFS	Progression free survival
PI3K	Phosphoinositide 3-kinase
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control

R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunomycin), Vincristine Sulfate (Oncovin), Prednisone – drug combination
RNA	Ribonucleic Acid
RP2D	Recommended Phase II dose
SAE	Serious Adverse Event/Serious Adverse Experience
SCT	Stem Cell Transplantation
SOP	Standard Operating Procedure
ULN	Upper limit of normal
US	United States
WHO	World Health Organization
WOCBP	Women of childbearing potential

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17 APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: GUIDELINES FOR PREGNANCY AND NURSING

Contraception

Copanlisib and/or rituximab may have adverse effects on a fetus in utero. Furthermore, it is not known if copanlisib or rituximab have transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if:

1. They are postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.); **OR**
2. They have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; **OR**
3. They have a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner by using a highly effective form of birth control while receiving copanlisib and for 30 days after the last dose of copanlisib:

Single method (highly effective)

- practice abstinence† from heterosexual activity
- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner while receiving rituximab and for 12 months after the last dose of rituximab by complying with the following:

Combination method (effective)

Requires use of two of the following:

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies

and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period and for at least 1 month after the last dose of copanlisib and 12 months after the last dose of rituximab, whichever is later, for WOCBP and for men. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Use in Pregnancy

If a subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Bayer without delay and within 2 working days to Bayer if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Bayer. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Bayer per the collaborative agreement.

Use in Nursing Women

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

APPENDIX C: THE LUGANO CLASSIFICATION RESPONSE CRITERIA

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: 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 (eg, 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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, 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 score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

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