Phase I/II Clinical Trial of Copanlisib and Ibrutinib in Mantle Cell Lymphoma
PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	All Protocol Activities
Monmouth	All Protocol Activities
Westchester	All Protocol Activities
Commack	All Protocol Activities

Nassau	All Protocol Activities

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: Phase I/II Clinical Trial of Copanlisib and Ibrutinib in Mantle Cell Lymphoma

Objectives: The objective of this trial is to determine toxicity, maximum tolerated dose and/or recommended phase II dose, and preliminary efficacy of the combination copanlisib and ibrutinib in patients with mantle cell lymphoma (MCL).

Patient Population: Patients with relapsed or refractory MCL with at least 1 prior line of therapy are eligible.

Study Design: This is a two stage protocol comprised of a single institution phase I dose escalation trial using standard 3+3 design and a phase II two stage Simon mini-max clinical trial.

Treatment Plan: Following enrollment, patients will be assigned to receive therapy with ibrutinib given by mouth daily and copanlisib given by intravenous injection once per week on days 1, 8, 15 of a 28 day cycle.

The phase II cohort will accrue patients at the MTD dose of copanlisib and ibrutinib determined during phase I. Patients will accrue in a two stage design and monitored for safety of copanlisib and ibrutinib combination therapy, duration of response, best response within 1 year, progression free survival, event free survival, and correlative biomarkers.

Time to Completion: In the phase I dose escalation portion of the study of 3 dose levels, a minimum of 4 patients and a maximum of 18 patients will be needed to complete this phase. The amount of time required to complete the dose escalation portion of this trial will depend on the number of dose levels studied and the number of patients accrued to each cohort. The phase II two stage Simon mini-max will enroll 18 patients in the first stage. If 5 or more patients have a complete response by 6 months, the trial will enroll to a total number of 33 patients. We anticipate enrolling 2-3 patients per month for an approximate accrual time of 2 years.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1. PRIMARY OBJECTIVES

- Phase I: Determine maximum tolerated dose and recommended phase II dose of copanlisib and ibrutinib combination
- Phase II: Determine complete response rate based on best response by 6 months for combination of copanlisib and ibrutinib

2.2. SECONDARY OBJECTIVE

- Phase I Dose Escalation and Phase II Dose Expansion Stages
    - Assess the efficacy as defined by overall response rate (best response within 1 year).
    - Assess the disease control rate (best stable disease, partial responses and complete response within 1 year).
    - Assess the duration of response for this population

- Assess the event free survival for this population
- Assess the progression free survival

2. 3. EXPLORATORY ASSESSMENTS

- Phase I Dose Escalation and Phase II Dose Expansion Stages
  - Determine the depth of response via targeted sequencing of peripheral blood circulating tumor DNA with combination targeted therapy
  - Correlate disease status, duration of response, PFS, and OS with sequentially measured ctDNA
  - Determine the pharmacokinetics of copanlisib and ibrutinib (phase I dose escalation only)

3.0 BACKGROUND AND RATIONALE

MCL is a unique subtype of NHL characteristic with the t(11;14) (q13;q32) balanced chromosomal translocation of the cyclin D1 gene (bcl-1) on chromosome 11 to the immunoglobulin heavy chain (IGH) enhancer region on chromosome 14, which results in Cyclin D1 over expression and increased cell proliferation of the tumor cells[1]. With a prevalence of 5% to 6% of all NHL, MCL accounts for up to 8000 newly diagnosed NHL cases in US and EU each year.

With the exception of rare patients who enjoy long term disease-free survival after non-myeloablative allogeneic stem cell transplantation, patients with MCL are not considered cured of their disease. Most MCL patients are treated with rituximab in combination with different chemotherapy regimens. The initial treatment usually yields a high response rate, however, most patients relapse following initial therapy and their median survival after relapse is about 1-2 years [2]. For relapsed MCL, ibrutinib is an FDA approved agent.

Ibrutinib in MCL has high response rates of 60-70%. However, the median duration of response is 18 months [3]. We can potentially improve response rates and duration of responses with combination therapy.

The BCR Pathway and ibrutinib

Chronic activation of the B cell receptor (BCR) pathway is essential for survival and proliferation of malignant B cells. Strong survival, cell proliferation and cell homeostasis pathways including Bruton's tyrosine kinase (BTK) mediated NF-κB activation and phosphatidylinositide 3-kinase (PI3K) triggered mTOR activation result from BCR engagement. Bruton's tyrosine kinase (BTK) functions as an intermediary between the BCR ligand activation and NF-κB activation in normal B cells.

Ibrutinib forms an irreversible covalent bond at cysteine 481 in the BTK active site to quench BTK tyrosine phosphorylation. The drug is well tolerated and shows strong activity in many lymphomas including mantle cell lymphoma (MCL), follicular lymphoma (FL) and diffuse large B cell lymphoma (DLBCL) (Table 3-1). A phase I study of ibrutinib in various B cell malignancies showed that ibrutinib was well tolerated with an excellent safety profile and was associated with an objective response rate of 60%.[4] Across five dose levels (1.25, 2.5, 5.0, 8.3, and 12.5 mg/kg/day), there were only 2 DLTs that occurred in 56 total patients (one grade 3 allergic hypersensitivity in a patient with a

history of drug hypersensitivity and one dose interruption for more than 7 days due to transient grade 2 neutropenia). There was no consistent relationship between dose level and adverse events. An MTD was not reached. Therefore, for an average 70 kg person, doses ranging from 87.5 mg/day to 875 mg/day were found to be safe in the phase I study. For further study in B cell non-Hodgkin lymphoma, an optimal biologic dose of 560 mg/daily was established and associated with full BTK receptor occupancy. Recently published phase II studies of ibrutinib also demonstrated that the drug is well-tolerated at a dose of 560mg/daily in mantle cell lymphoma and 420 mg/daily in chronic lymphocytic leukemia [5, 6].

In R/R MCL, a phase II study of 111 patients showed an overall response rate of 68% while the majority of responses seen were partial responses (47%) [3]. The median duration of response was 17.5 months with a PFS of 13.9 months [3]. In a small phase I study of FL, 16 patients treated with ibrutinib demonstrated an ORR of 55%, median PFS 13.4 months [7]. In DLBCL, the effectiveness of ibrutinib was seen primarily in non-GCB subtype. When analyzing both the non-GCB and GCB DLBCL responses, the ORR in DLBCL was 21.7% [8]. However, the non-GCB DLBCL subgroup showed an ORR of 40% with a median PFS of 5.5 months [8].

Clearly, ibrutinib has definitive clinical activity and improvements can be made to prolong overall response, duration of response (DOR) and progression free survival (PFS). Logically, ibrutinib is suitable for combination with other targeted therapies with broad single agent activity such as PI3K inhibitors (Table 3-1).

Table 3-1. Overall response rates of ibrutinib

Drug	Target	Mantle Cell Lymphoma	Follicular Lymphoma	DLBCL
		ORR	ORR	ORR
Ibrutinib	BTK	68%[3]	55%[7]	21.7%, 40% (non-GCB) [8]

The PI3K pathway and copanlisib

The class I PI3K pathway includes four isoforms: PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ [9]. PI3Kδ and -γ expression is largely limited to leukocytes while PI3K-α and -β are ubiquitously expressed [10]. PI3Kα mutations and amplifications have been identified across multiple cancer subtypes and both overexpression of PI3Kα and gain of function PI3Kα mutations were found to be oncogenic [11-14]. PI3Kα is also the primary isoform required for insulin signaling [15]. PI3Kβ isoform has roles in regulating formation and stability of integrin which is required for platelet activation [16]. PI3Kδ and -γ regulate leukocyte trafficking and cell proliferation [17-20]. Mice with functionally deficient PI3Kδ have impaired immune systems with abnormal antibody development and inflammatory bowel disease [20]. However, dissecting the individual function of class I PI3K isoforms have been complicated by the heterodimeric nature of the proteins as altering expression of one subunit affects the expression profile of others.

Multiple PI3K inhibitors have been in development for B-cell non-Hodgkin lymphoma (NHL) (Table 3-2). Idelalisib, a delta specific PI3K inhibitor, was the first and currently the only PI3K inhibitor with regulatory approval in relapsed/refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) and follicular lymphoma (FL). Chronic administration of idelalisib is associated with low but clinically meaningful risk of transaminitis, pneumonitis, colitis, and

opportunistic infections [21]. Duvelisib, a PI3K δ and γ inhibitor, demonstrated approximately 50% overall response rate in indolent NHL with a 10 month median duration of response [22]. Dreyling et al. reported on the safety and efficacy of copanlisib, a pan PI3K inhibitor with primarily α and δ activity, in relapsed/refractory B-cell NHL. Clinical response rate is 59% in FL, and 64% in mantle cell lymphoma (MCL)[23, 24]. Most commonly observed adverse events were hyperglycemia (49%), hypertension (29%), fatigue (12%), and diarrhea (18%). The availability of a PI3Kα/δ inhibitor in the form of copanlisib allows us to dissect the relevance of specific PI3K isoforms in lymphoma. Potentially, the dual PI3K α/δ inhibition by copanlisib blocks compensatory resistance mechanisms to PI3K inhibitors.

Table 3-2. Efficacy of PI3K inhibitors in lymphoma

Drug	Target	Admin	Disease	CLL	FL	MZL	SLL	DLBCL / Tx FL	MCL
Copanlisib [23, 24]	Pan-PI3K Predominantly alpha, delta	IV	N	13	104	23	8	67	11
			CR/PR	0/5	15/46	2/14	0/6	5/8	2/5
			ORR	38.5%	58.7%	69.9%	75%	19.4%	63.6%
			DoR	Indolent – 12.8 mo			Aggressive – 5.46 mo		
Buparlisib [25]	Pan-PI3K	PO	N					26	20
			CR/PR					1/2	1/4
			ORR					11.5%	25%
			DoR					NA	NA
Idelalisib [26-29]	Delta	PO	N	88 (+ Rituximab)	72	15	28		40
			CR/PR	0/71	6/33	1/5	0/15		2/14
			ORR	81%	54%	47%	61%		40%
			DoR	Median NR	Median NE	NA	11.9 mo		2.7 mo
Duvelisib (IPI-145) [22]	Delta, Gamma	PO	N		83	18	28	10	
			CR/PR		1/35	0/6	0/19	0/0	
			ORR		41 %	33%	68%	0%	
			DoR		7.9 mo	8.3 mo	10.1 mo	NA	

CR - complete response, PR – partial response, ORR – overall response rate, DoR – duration of response, NR – not reached, NE – not evaluated, NA – not available

Various models support the importance of multiple PI3K isoforms in lymphomagenesis. In one model of resistance to PI3K inhibitors, primary mantle cell lymphoma patient samples demonstrated compensatory increase of PI3Kα in the relapsed setting [30]. In addition, while PI3Kδ inhibition reduced B-cell receptor induced PI3K activation, dual inhibition of PI3Kα and –δ was required for effective blockade of PI3K signaling[30]. Increased protein expression and copy number gains of PI3Kα have also been identified in various lymphomas indicating a role of PI3Kα in lymphomagenesis [31, 32]. Furthermore, two independent studies support the importance of dual PI3Kα and –δ inhibition. Using a PI3Kα shRNA knockdown model, DLBCL cell lines are more sensitive to dual inhibition of PI3Kα and –δ blockade [33]. Similar studies using PI3K isoform specific inhibitors demonstrate that combination of PI3Kα and –δ inhibition is required for suppression of phospho-AKT, and downstream NFkB and PI3K pathways [31, 33]. Resistance to PI3K δ inhibition may be overcome by concurrent PI3Kα inhibition [33].

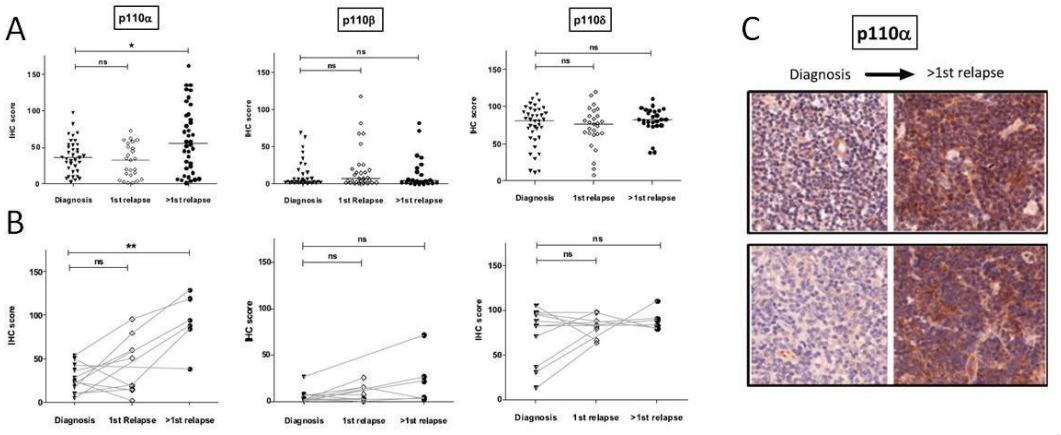


Figure 3-1. IHC expression of PI3K isoforms in MCL. A) Immunohistochemistry of PI3Kα, PI3Kβ, and PI3Kδ at diagnosis, first relapse and beyond first relapse. B) 12 sequential cases of patients with paired biopsies showing increasing PI3Kα with disease progression. C) Representative IHC staining at 200x of sequential biopsies from two patients showing significant increase in PI3Kα expression at relapse. [30]

Synergy of PI3K and BTK inhibitors

In vitro combinatorial screens identified PI3K inhibitors and BTK inhibitors as strongly synergistic [34]. A patient derived xenograft model demonstrate that combination of BTK and PI3K α/δ inhibition is more active compared to BTK inhibition alone [33]. An observed rebound activation of AKT and BTK associated with isolated PI3K or BTK inhibition provides a mechanistic rationale for synergy between PI3K and BTK inhibitors in diffuse large B cell lymphoma [31]. Thus, PI3K inhibitor such as copanlisib may be suitable for combination with BTK inhibitors such as ibrutinib.

Two early phase studies using PI3K and BTK inhibitors demonstrate the feasibility of this approach [35, 36]. Both buparlisib, an oral pan-PI3K inhibitor, and umbralisib (TG-1202), an oral PI3K delta inhibitor have been combined with the BTK inhibitor ibrutinib with promising efficacy in CLL and MCL [35, 36]. The phase I/II study of buparlisib, a pan-PI3K inhibitor, and ibrutinib (protocol 16-009) at MSK showed high clinical activity in mantle cell lymphoma. Of 11 treated patients thus far, the overall response rate is 100% with 9 complete responses and 2 partial responses. Two independent preclinical studies investigating the combinations of copanlisib and ibrutinib and a PI3Kα/δ inhibitor and ibrutinib generated promising activity specifically in ABC-DLBCL [16, 33]. Therefore, a molecularly based evaluation of PI3Kα/δ and BTK inhibition is a promising approach for treatment of lymphoma.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a phase I/II, open label single institution trial. The phase I study is a standard 3 x 3 dose escalation trial to assess the safety of combination therapy with copanlisib and ibrutinib. We will enroll a dose escalation cohort treating patients with copanlisib and ibrutinib at escalating doses.

A maximum number of 18 patients will be enrolled in this stage. This will determine the maximum tolerated dose and the recommended phase II dose.

In the phase II study, the cohort will expand and accrue patients at the recommended phase II dose of copanlisib and ibrutinib determined during phase I dose escalation. In a simon two stage mini-max design, an initial 18 patients will be enrolled, inclusive of 6 patients treated at MTD or RP2D from phase I study, in first stage. If 5 or more patients have a complete response by 6 months, then an additional 15 patients will be enrolled for a total accrual of 33 patients.

4.3 Intervention

Treatment will be with intravenous copanlisib on days 1, 8, 15 of 28 day cycles and oral ibrutinib daily in 28 day cycles. A cycle is defined as 28 days of therapy. If patients are in a CR by RECIL criteria, copanlisib will be held after 2 cycles of combination past a CR or minimum of 6 cycles of therapy. Copanlisib will be restarted upon radiographic and pathologic progression of disease (see Section 9.9). Patients remain on continuous ibrutinib if copanlisib is held. It may then be restarted as clinically indicated. Therapy will continue until disease progression, intolerable toxicities or death with a maximum duration of treatment of 36 cycles not exceeding 36 months on therapy.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. Copanlisib

Copanlisib, also known as BAY 80-6946, is an intravenously-administered, small-molecule inhibitor of PI3K manufactured by Bayer. The copanlisib IND will be cross referenced between MSKCC and Bayer. IND approval and activation is pending at MSKCC.

Physical Description of Study Drug(s): Copanlisib lyophilisate 60 mg 1.5 mL for injection 001 is a single use container.

Labeling: Study drug labels will contain information to meet the applicable regulatory requirements. The investigational products will be labeled as open-label material.

Preparation, Handling, and Storage:

Copanlisib is a lyophilized preparation filled in 6-mL injection vials. Due to the technically required overfill the total amount is 68.4 mg Copanlisib per vial. After reconstitution with 4.4 mL of 0.9 % NaCl solution a total volume of 4.55 mL is obtained. The resulting drug substance concentration is 15 mg/mL Copanlisib. To obtain the target dose of copanlisib a volumes of 2.0 - 4.0 mL has to be withdrawn (Table 5-1). Withdraw the required amount of the reconstituted lyophilisate with an unused sterile syringe. Connect the syringe to the patient infusion bag with 100 mL 0.9 % NaCl solution. Transfer the required amount of the reconstituted lyophilisate into the bag.

Table 5-1. Copanlisib dose based on reconstituted copanlisib solution			
Copanlisib dose [mg]	30	45	60
Reconstituted Copanlisib solution [mL]	2	3	4

Chemical and physical in-use stability of reconstituted and diluted solution has been demonstrated for 24 hours at 2 °C to8 °C and room temperature. However, from a microbiological point of view, the solution product should be used immediately. If not used immediately, the time prior application should normally not be longer than 24 hours at 2 °C to 8 °C (refrigerated). It takes approximately 60 minutes for the 100 mL dilution filled in bags to return to room temperature after refrigeration.

Please refer to the pharmacy manual for detailed instructions for the reconstitution of the lyophilisate and dilution of the reconstituted solution. Please refer to the investigator's brochure for copanlisib for more details regarding drug properties and formulation.

5.2. Ibrutinib

Ibrutinib is an orally-administered, small-molecule inhibitor of BTK manufactured by Janssen, and co-developed by Janssen and Pharmacyclics. The ibrutinib will be commercially available based on an approved FDA indication.

Physical Description of Study Drug(s): Ibrutinib tablets are debossed with "ibr" on one side and the strength in milligrams on the other side (ie, "420", "560"). Each 420mg tablet is a yellow green to green oblong tablet. Each 560mg tablet is a yellow to orange oblong tablet.

Packaging: Ibrutinib tablets will be packaged in a carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets with labels bearing the appropriate label text as required by governing regulatory agencies.

Labeling: Study drug labels will contain information to meet the applicable regulatory requirements. Each carton of ibrutinib will contain a study specific label.

Preparation, Handling, and Storage: Study drug will be stored at the study site in a secure area with restricted access until dispensed to the study subjects. Tablets will be stored in the original packing at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package until dispensing. If a drug shipment arrives damaged, or if there are any other drug complaints, Janssen will replace the drug. Tablets are stable in their packaging until the indicated expiration date. The study drug may be destroyed at the study site per the local SOPs/policies. Refer to the USPI for additional information regarding storage and handling of ibrutinib.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

Patients eligible for inclusion in this study have to meet **ALL** of the following criteria:

- Patient is ≥ 18 years of age at the time of signing Informed Consent
- Patient is able and willing to adhere to the study visit schedule and other protocol requirements
- Patient has histologically confirmed diagnosis of R/R mantle cell lymphoma who has received at least 1 line of therapy

  - Autologous stem cell transplant recipients must have adequate bone marrow recovery and transfusion independent
- Patients may have been previously treated with BTK or PI3K inhibitors:
  - If BTK/PI3K inhibitors were part of their last treatment, patients must have had a best response of stable disease or better.
- Patient has at least one measurable lesion (≥ 2 cm) according to RECIL criteria[37]
- Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Patient has adequate bone marrow and organ function by:
  - Absolute neutrophil count (ANC) ≥ 1 x 10^9/L , independent of growth factor support for 14 days unless there is bone marrow involvement. For patients with bone marrow involvement, ANC ≥ 500/uL independent of growth factor support for 14 days
  - Platelets ≥100 x 10^9/L, or ≥50 x 10^9/L if bone marrow involvement and independent of transfusion support for 14 days in either situation
  - Hemoglobin (Hgb) ≥ 9.0 g/dL (no RBC transfusion within past 14 days)
  - International Normalized Ratio (INR) ≤ 1.5
  - Serum Creatinine ≤ 1.5 x upper limit of normal (ULN) or creatinine clearance ≥ 25 mL/min as determined by the Cockcroft-Gault equation or a 24 hour urine collection
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ ULN (or ≤ 3 x ULN if liver involved with disease
  - Total serum bilirubin ≤ ULN (or ≤ 1.5 x ULN if documented hepatic involvement; or total bilirubin ≤ 3 x ULN with direct bilirubin ≤ 1.5 x ULN in patients with documented Gilbert's Syndrome.
  - Lipase ≤ 1.5x ULN
  - LVEF ≥ 50%
  - Hemoglobin A1c ≤ 8.5%

6.3 Subject Exclusion Criteria

Patients eligible for this study must **NOT MEET ANY** of the following criteria:

- Patient has a history of non-compliance to medical regimen or inability to grant consent
- Patient is concurrently using other approved or investigational antineoplastic agent with the exception of BTK or PI3K inhibitors in patients who had these agents as the last line of treatment
  - Patients on BTK or PI3K inhibitors will be continued on therapy as they transition to protocol therapy
- Patient has not recovered to Grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy
- Patient has had major surgery or a wound that has not fully healed within 4 weeks of starting study drugs.

- Patients who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.
- Patients who have undergone an allogenic hematopoietic stem cell transplant
- Patient has active or history of central nervous system (CNS) disease or meningeal involvement.
- Patient has history of clinically significant interstitial lung disease and/or lung disease that severely impairs lung function (as judged by the investigator)
- Patient has history of stroke or intracranial hemorrhage ≤ 6 months from starting study drugs.
- Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- Patient has clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification, Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO), unstable angina pectoris, symptomatic pericarditis, QTcF > 480 msec on the screening ECG (using the QTcF formula)
- Patient has a concurrent active malignancy. Malignancies treated with a curative intent with an expected life expectancy ≥ 5 years or a non-competing life expectancy risk are eligible (i.e. adequately treated basal or squamous cell carcinoma, non-melanomatous skin cancer, early stage breast cancer, treated prostate cancer or any other cancer from which the patient has been disease free for ≥ 3 years).
- Patient with known history of human immunodeficiency virus (HIV), or any uncontrolled active systemic infection.
- Patient has CMV viremia (peripheral blood CMV PCR positive), acute viral hepatitis (typically defined by elevated AST/ALT), or a history of chronic or active HBV or HCV infection. HBV infection is defined as having HBsAg and/or HBcAb positive test with concurrent detectable HBV DNA levels. HCV infection is defined as detectable HCV RNA levels.
- Patient requires treatment with a strong or moderate cytochrome P450 (CYP) 3A4 inhibitors, and inducers, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. Moderate and strong CYP modulators (inducers and inhibitors) should have a washout period of at least 5-6 half-lives before initiating ibrutinib or copanlisib.
- Patients with known bleeding diathesis (e.g. von Willebrand ‘s disease) or hemophilia
- Patient is currently receiving warfarin or other Vitamin K antagonist. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed. Refer to Section 9.5 for Concomitant medication
- Patients with Child Pugh Class B or C hepatic cirrhosis
- Patients with any life threatening illness, medical condition or organ system dysfunction that in the opinion of the investigator could compromise the subject’s safety, interfere with absorption of metabolism of study drugs or put the study outcomes at undue risk.

7.0 RECRUITMENT PLAN

The study will be conducted at Memorial Sloan Kettering Cancer Center. Patients will be treated by the lymphoma service at MSKCC. Every effort will be made to include women and minorities in this research study. Patients will be recruited by the treating team of physicians and medical professionals. The consenting attending physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits, and experimental nature of this treatment program. All patients will be required to sign a statement of informed consent that conforms to FDA and IRB guidelines.

8.1 PRETREATMENT EVALUATION

Prior to initiating treatment:

- Prior biopsy with pathologic confirmation of MCL.
- Archival block 10-15 x 10 micron unstained slides and 1 H&E will be requested. A minimum of 40 micron material is requested.
- If archival tissue is not available, patients will be asked to provide informed consent for an optional repeat biopsy.

Within 4 weeks prior to initiating treatment:

- Medical history and demographics
- Complete history and physical exam (including weight, pulse, blood pressure, temperature, ECOG performance status)
- Medication review
- Hepatitis B surface antigen and Hepatitis B core antibody (HBV DNA PCR is only required if HBsAg is positive)
- Hepatitis C antibody
- HIV testing
- Cytomegalovirus PCR testing
- ECG
- Echocardiogram or MUGA to evaluate cardiac function
- PET scan
- CT chest/abdomen/pelvis and neck CT if clinically indicated (MRI will be used for those who are unable to undergo CT scans).

Within 1 week prior to initiating treatment:

- Blood work: CBC with differential, PT/INR, electrolytes (Na, K, Cl, CO_2), BUN, Cr, total bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase, uric acid, LDH, magnesium, phosphorus, lipid panel, thyroid function tests, hemoglobin A1c, fructosamine, amylase, lipase, urinalysis, GFR
- Serum beta-HCG (for WOCBP only) to assess for pregnancy

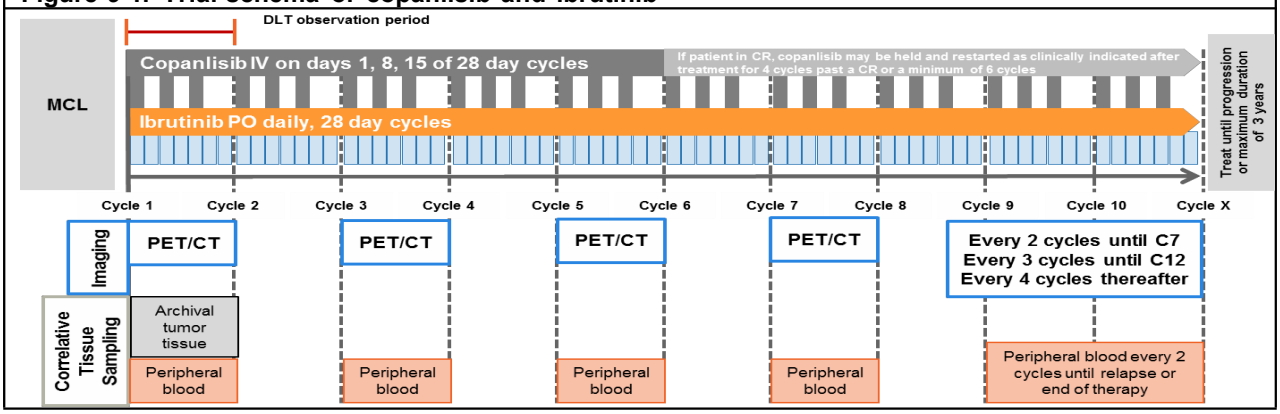
9.0 TREATMENT/INTERVENTION PLAN

9.1. Study Treatment

The investigational agents to be used in this study are copanlisib and ibrutinib. Copanlisib is given intravenously on days 1, 8, and 15 of 28 day cycles. Ibrutinib is given orally every day on 28 days cycles. The maximum duration of treatment is 36 cycles not exceeding 36 months. Dose changes or interruptions are allowed per below guidelines and must be recorded appropriately.

Study personnel will maintain a log of all drugs supplied to the patient. Drug supplies for each patient will be inventoried and accounted for. Subjects will be given diary cards to complete for the ibrutinib taken at home. Subjects must bring the diary cards to the site on every visit so study site personnel can verify compliance.

Figure 9-1. Trial schema of copanlisib and ibrutinib



9.1.1 Copanlisib administration:

Copanlisib is supplied as lyophilized preparation in a 6-mL injection vial. The total amount of copanlisib, BAY 80-6946, per vial is 60 mg. The solution for IV infusion is obtained after reconstitution of the lyophilisate with 0.9% sodium chloride solution. Please refer to the Pharmacy Instructions for detailed instructions for the reconstitution of the lyophilisate and for further dilution of the reconstituted solution. Study drug is administered in a normal saline solution, intravenously, over 1 h (or per MSK protocol). No intravenous glucose preparations should be administered on the days of infusion. Dosing is weekly for the first 3 weeks of a 28-day cycle (on Days 1, 8, and 15), followed by a 1-week break (i.e., no infusion on Day 22). Patients will be on 30 mg, 45 mg or 60 mg depending on their dose level.

Laboratory blood tests on day 1 of copanlisib treatment must follow the below criteria:

Table 9-1: Laboratory test criteria for Day 1 dose of subsequent cycles	
Laboratory Test	**Criteria for Day 1 dose (Cycle 2 and higher)**
Glucose	< 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)
Hemoglobin	≥ 8 g/dL [a]
ANC	≥ 1 x 10^9
Platelets	≥ 75 x 10^{9b}

ANC = Absolute neutrophil count;
a: If hemoglobin is < 8 g/dL but ≥ 6 g/dL on the day of planned study drug administration it is permissible to give the study drug dose as scheduled and transfuse within 48 hours after the dose, if the patient is hemodynamically stable and in opinion of investigator benefits outweigh risks. Rationale and treatment should be recorded in source document and eCRF.
b: If Platelets is <75 x 10^9 but ≥ 50 x 10^9 on day of planned study drug administration, it is permissible to give study drug if this is related to disease.

Glucose Monitoring for copanlisib administration

Treatment – Cycle 1

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, patients should be fasting for at least 8 h prior to the pre-dose glucose measurement. Fasting glucose should be < 125 mg/dl for non-diabetic patients or <160 mg/dl for diabetic patients.
- Glucose will be measured at 0 h (pre-dose) and post dose 1 hour and 2 hours after the end of copanlisib infusion (deviation of ± 15 min is allowed). Additional measurements to be performed at the clinic as clinically indicated.

NOTE: Patients should be educated on the signs and symptoms of hyperglycemia, suchas frequent urination, increased thirst, blurred vision, headaches and difficulty concentrating and must report these to the investigator or their physician immediately. If patient needs to take a meal, then glucose test should be taken prior to meal intake.

Cycle 1 Day 8, Cycle 1 Day 15, and all subsequent doses

- Fasting is not required before first glucose measurement.
  - If patient is fasting, glucose should be <160 mg/dl prior to copanlisib infusion
  - If patient is non-fasting, glucose should be <200 mg/dL prior to copanlisib infusion
- Glucose will be measured prior to and after the end of copanlisib study drug IV infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement). Patients are not required to be fasting prior to pre-dose glucose measurement.

Blood pressure measurement on treatment days

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 patient 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 min (mid-infusion), 60 min (end of infusion), and 1 h and 2 hours after the end of infusion

Note: a window of ±10 min is allowed for all BP measurements

Ibrutinib administration:
Ibrutinib will be administered once daily continuously until disease progression, intolerance, or completion of 36 cycles, not exceeding 36 cycles since start of therapy whichever comes first. Patients will be instructed to take 420 mg or 560 mg depending on the treating cohort.

Ibrutinib should be administered at about the same time each day orally with 8 ounces or approximately 240 mL of water. The drug should be swallowed intact and subjects should not attempt to crush dissolve the tablets in water. If a dose is missed, the dose may be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra tablets of ibrutinib should not be taken to make up for the missed dose. If a patient vomits the dose, the dose should not be retaken. On days when patients are receiving copanlisib and ibrutinib, patients should take their dose of ibrutinib in clinic just prior to the copanlisib infusion.

9.2. Definitions of dose limiting toxicity, maximum tolerated dose, and recommended phase II dose

A dose limiting toxicity (DLT) is defined as any of the following adverse events occurring within cycle 1 (28 days). A maximum tolerated dose (MTD) is defined as the highest dose studied for which the incidence of DLT is less than 33%. The recommended phase II dose (RP2D) is the dose with clinical efficacy without major toxicity.

- Any AE resulting in a dose delay of >7 consecutive days within the DLT period based on dose modifications in Table 9-6
- Non hematologic AE:
    - Hemorrhage requiring transfusion or procedural intervention, intracranial hemorrhage, intraocular hemorrhage of any grade
    - Grade 4 arterial hypertension
    - Any Grade ≥3 AE EXCEPT noted below
        - Grade ≥ 3 nausea, vomiting, constipation or diarrhea persisting for <48 hours
        - Grade ≥3 rash or skin hypersensitivity persisting for <7 days
        - <7 days of Grade ≥3 fatigue
        - <7 days of Grade ≥ 3 edema
        - <7 days of post infusion blood glucose >250mg/dL despite optimal glucose management or <2 days of blood glucose >500mg/dL despite optimal glucose management

- Grade 3 (or 4) isolated electrolyte abnormalities that resolve, with or without intervention, to Grade ≤ 2 in less than 72 hours Hematologic AE
    - Any Grade 4 neutropenia lasting more than 7 consecutive days
    - Febrile neutropenia ≥ Grade 3 (ANC <1000/mm3 with a single temperature of >38.3C or a sustained temperature of ≥ 38C for more than 1 hour
    - Grade 4 thrombocytopenia lasting more than 7 days or Grade 3 thrombocytopenia with evidence of ≥ Grade 2 bleeding
- Any Grade 5 toxicity is considered a DLT.

9.3. Phase I dose escalation phase

Cohorts of 3-6 patients each will be treated with escalating doses of copanlisib and ibrutinib (Table 9-2). If unforeseen toxicities are observed in 2 patients treated at dose level 1, the next cohort will be treated at dose level -1.

Table 9-2. Dose Escalation Levels

No of pts	Cohort Level	Copanlisib (mg/dose)	Ibrutinib (mg/day)
3-6	-1	45	420
3-6	1	45	560
3-6	2	60	560

- At least 2 patients will be treated at each dose level. All patients treated at the preceding dose level will be observed at minimum of 28 days (1 cycle) before dose escalation occurs.
- Dose escalation will proceed as follows:
    - If none of the initial 3 patients in a cohort experiences dose limiting toxicity (DLT), then a new cohort of 3 patients will be treated at the next higher dose level.
    - If one of 3 patients in a cohort experiences DLT, then up to an additional 3 patients will be treated at the same dose level. Escalation will continue if only one of the 6 patients experiences a DLT.
    - In the event that ≥2 of 3 patients, or ≥2 of 6 patients in the first cohort experiences a DLT related to study drugs, then the next cohort of patients will be treated at a lower dose level (dose level -1) and no further dose escalation will occur in this step. Three patients will be enrolled at this dose level, if 0 or 1 patients experiences a study drug related DLT, a further 3 patients will be enrolled at this dose level. If overall 0 or 1 patient experiences a DLT at this dose level, this dose will be established as copanlisib/ ibrutinib maximum tolerated dose (MTD).
    - If ≥2 or more patients in the cohort experience DLT, then the maximum tolerated dose (MTD) will have been exceeded, and no further copanlisib and ibrutinib dose escalation will occur. The previous dose will be considered as the MTD.
    - If only 3 patients were treated at the dose level under consideration as the MTD, then up to an additional 3 patients will be accrued. If no more than 1 of 6 patients at that copanlisib and ibrutinib dose level experiences DLT, than that dose level will be confirmed as the MTD. If ≥2 or more patients in that cohort experience DLT, than the previous dose level will be studied in the same fashion.

The maximum tolerated dose (MTD) is the highest combination drug dosage not causing medically unacceptable DLT in ≥33% (i.e. 2/6 patients) in the first cycle of treatment. The recommended phase II dose (RP2D) is the dose balancing clinical efficacy and toxicity.

9.4. Phase II dose expansion

Patients will be enrolled at the MTD of copanlisib and ibrutinib combination. The safety events in the expansion cohorts will be reviewed on an ongoing basis by the primary investigator and several stopping rules are in place to protect patients from excessive toxicity (Section 14). Based on this review, we may adjust treating dose level to the RP2D.

Table 9-3. Phase II Simon two stage mini-max dose expansion cohorts

Disease	1st stage	Response Needed	2nd stage	Total Accrual
Mantle cell lymphoma	18 (include 6 patients from phase I study at MTD/RP2D)	If ≥5 patients with CR within 6 months, proceed to 2nd stage	15	33 patients

9.5. Pharmacokinetics

Plasma concentrations of copanlisib, its metabolite M-1, and other metabolites if needed, and of ibrutinib will be measured at the following time points for pharmacokinetic (PK) assessment of patients in the phase I dose level 1 and 2 cohorts (see Table 9-4).

Table 9-4. Pharmacokinetic assessments

Cycle	Day	Planned time (h) after start of administration	Acceptable time window	Ibrutinib PK sampling	Copanlisib PK sampling	Ibrutinib dosing	Copanlisib dosing
1	15	0 (pre-dose)	- 30 min	X	X	X	X
		1 (end of Infusion) [a]	+ 5 min	X	X		
		1.5	± 15 min	X	X		
		2.5	± 30 min	X	X		
		3.5	± 30 min	X	X		
		4.5	± 30 min	X	X		
		6	± 30 min	X	X		

C_{max} = Maximal plasma concentration; EoI = End of infusion; PK = Pharmacokinetic(s).
a: The end of infusion sample for copanlisib and M-1 metabolite should be collected within 5 min after the end of infusion (EoI) of copanlisib for adequate characterization of C_{max}.

Samples should be collected at the planned time points as per Table 9-4, ideally within the allotted time windows. If samples are drawn outside the time window, it will not be considered a protocol deviation but the actual time of the blood draw should be noted. If clinically indicated, PK samples may be skipped without being considered a protocol deviation. For all samples, it is of importance that the actual date and time of blood sampling are documented in the eCRF because PK calculations will be based on the actual sampling times relative to dosing times.

Details about the collection, processing, storage and shipment of samples are provided separately in the Laboratory Manual.

9.6. Concomitant Medications

9.6.1 Permitted Concomitant Therapy

- Standard therapies for concurrent medical conditions
- Treatment with non-conventional therapies (for example herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator. St John's Wort is not permitted.
- Bisphosphonates
- Close monitoring is recommended according to standard of care. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until it is stable.
- Antiemetics: Prophylactic anti-emetics may be administered according to standard practice. The routine use of standard antiemetics, including steroids, 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed.
- Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all patients in this trial.
- Patients may receive palliative and supportive care for any underlying disease
- Palliative irradiation shall be permitted provided that:
    - In the opinion of the investigator, the patient does not have progression of disease.
    - The radiation field does not encompass a target lesion
    - The radiation field does not encompass a lung field (to reduce the risk for pneumonitis).
- Low-dose aspirin (maximum 100 mg/day) and low-dose heparin are permitted.
- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine, cyclosporine, and digoxin
- Short term systemic corticosteroids will be allowed for the management of acute conditions
- Use of neutrophil growth factors (filgrastim and pegfilgrastim) is not permitted in the dose escalation phase during cycle 1 unless a DLT has already been determined. Neutrophil growth factor support is allowed in the dose expansion portion of the study to treat neutropenia but not prophylactically.

9.6.2 Prohibited Concomitant Therapy

The following medications are prohibited during study treatment in the study (see Table 9-5 below):

This list is not comprehensive and is only meant to be used as a guide:

- Strong inhibitors or inducers of CYP3A4/5
- Other investigational and antineoplastic therapies
- Anti-arrhythmic therapy other than beta blockers or digoxin
- Ongoing immunosuppressive therapy
- Concomitant radiotherapy (it is assumed that radiation would be indicated only in case of progression, when the patient would come off study medication anyway)

- Herbal medications include, but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications at least 7 days prior to first dose of study treatment.

Table 9-5: List of prohibited medications during the study

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)
Other Investigational and Antineoplastic Therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.
Herbal Preparations/ Medications	Herbal preparations/medications should be reviewed for appropriateness and interactions throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug
Palliative Radiotherapy	No dose modification of study treatment is needed during radiotherapy.

9.6.3 Drug-drug Interactions

Guideline for Use of CYP Inhibiting/Inducing Drugs

Both ibrutinib and copanlisib are metabolized primarily by CYP3A4. Plasma concentrations of ibrutinib and copanlisib may be increased from concomitant use of strong or moderate CYP3A4 inhibitors. . Consequently, strong or moderate CYP3A4 inhibitor and inducers should be avoided. Ibrutinib and its major metabolite (dihydrodiol) have been shown, in vitro, to be weak inhibitors and inducers of CYP450 isoenzymes. Note that with the data available, it is not possible to confirm whether such interactions will occur in patients. Therefore, investigators, at their discretion, may administer concomitant medications known to be metabolized by

CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. The use of moderate and strong CYP3A inducers and inhibitors is strictly prohibited during the DLT evaluation period.

During phase II, strong inhibitors of CYP3A suchas ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazodone, etc should be avoided. If strong CYP3A inhibitors cannot be avoided, consider holding ibrutinib and copanlisib while on CYP3A inhibitor if it will be used short-term. Re-initiate ibrutinib and copanlisib after 5 to 6 half-life washout period of the CYP3A inhibitor. If concurrent therapy with strong inhibitors cannot be avoided, reduce the copanlisib dose to 45 mg. If antifungal therapy is required, strong inhibitors of CYP3A4, including ketoconazole, itraconazole, posaconazole, and voriconazole should be avoided. Moderate inhibitors of CYP3A4, such as isavuconazonium sulfate, may be used. If used with a moderate CYP3A4 inhibitor, ibrutinib dosing should be reduced to 140 mg daily. No dose adjustment to copanlisib is needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix 1).

During phase II, strong inducers of CYP3A such as enzyme-inducing anti-epileptics (carbamazepine, phenytoin, etc), rifampin, and St. John's Wort etc, should be avoided. Co-administration of ibrutinib with strong CYP3A inducers, rifampin, in healthy subjects decrease ibrutinib plasma concentrations by approximately 10-fold. Consider alternative agents with less CYP3A induction. If strong CYP3A inducers cannot be avoided, consider holding ibrutinib and copanlisib while on CYP3A inducer if it will be used short-term. Re-initiate ibrutinib and copanlisib after 5 to 6 half-life washout period of the CYP3A inducer. Additionally, corticosteroid doses more than 4mg oral daily of dexamethasone-equivalent (>26mg prednisone) may induce CYP3A enzyme, so need to be discussed with investigators.

A list of common, moderate to strong, CYP3A inhibitors or inducers is provided in the appendices; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates (Appendix 1).

Sensitive substrates of CYP3A should be used with caution. A comprehensive list of sensitive substrates of CYP3A could be found on FDA website: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table3-1.

Concomitant Use of Antiplatelet Agents and Anticoagulants

Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. The mechanism for this bleeding is not well understood.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib or copanlisib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function.

Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising and ibrutinib should be withheld in the event of any bleeding events.

Subjects requiring the initiation of anticoagulation therapy (other than warfarin or a vitamin K antagonist, which should be avoided) during the course of the study should have treatment with ibrutinib held, the PI should be contacted, and ibrutinib should not be restarted until the subject is clinically stable. Subjects should be observed closely for signs and symptoms of bleeding.

Subjects were excluded from participation in ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Therefore, ibrutinib should not be administered concomitantly with warfarin or other vitamin K antagonists. Ibrutinib should be used with caution in patients requiring other anticoagulants or medications that inhibit platelet function. Patients receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided. Patients with congenital bleeding diathesis have not been studied.

9.7. Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v5.0 used as a guide for the grading of severity. Prior to completion of cycle 1 in both dose escalation or dose expansion phase, treatment with either ibrutinib, copanlisib or both may be interrupted for ≤ 7 days for any reason and then resumed at the same dose. If patients take less than 2 infusions of copanlisib or less than 14 days of ibrutinib during the intended dose of cycle 1, they will be excluded from the DLT analysis and replaced. However if a patient takes less than 14 days of the intended dose of cycle 1 due to a DLT, they will be included in the DLT analysis and not replaced. After completion of cycle 1, study drugs (either ibrutinib, copanlisib) may be interrupted for ≤ 28 days for any reason and then resumed at same or reduced dose. The investigator may remove any patient from study for any toxicity if the investigator believes it is in the best interest of the patient to discontinue study treatment.

Intrapatient dose reduction will not be allowed during cycle 1 unless a DLT has occurred and been counted. This is in order to accurately determine the safe and tolerable dose of copanlisib when used in combination with ibrutinib. Dose reductions may be made to ibrutinib and/or copanlisib during cycles 2 and beyond. If a toxicity can be ascribed to a specific study drug, then that drug may be dose modified while the non-offending drug may be maintained. Whether to dose modify ibrutinib or copanlisib is at the discretion of the treating physician.

If the patient experiences unacceptable toxicity that fails to resolve after a maximum dose delay of 28 consecutive days, then the patient should be discontinued from the study treatments. In cases of treatment delays from reactivation of CMV, treatment delays can be extended for up to 2 months. In exceptional situations, if the patient is clearly benefiting from the study treatment (i.e. stable disease or better) and in the opinion of the investigator no safety concerns are present, the patient may remain on the study treatment. Patients who discontinue from study for a study related adverse event or an abnormal laboratory value must be followed as described in Section 10.

Each patient is allowed a maximum of two dose reduction of each study drug. Dose reduction of copanlisib or ibrutinib indicates treatment at the next lower dose of copanlisib or ibrutinib based on Table 9-6. If after treatment interruption, resolution of toxicity, and treatment resumption at same dose, the subject presents with the same toxicity at the same severity, then the next treatment re-

initiation must resume at the next lower dose level irrespective of duration. A patient must discontinue therapy if after therapy is resumed at a lower dose, the same toxicity recurs with the same or worse severity. Copanlisib and ibrutinib dose modification guidelines for specific toxicities are outlined in Table 9-7.

Table 9-6. Intrapatient dose reduction*

Drug	Maximum Dose Levels	Reduction Dose Level 1	Reduction Dose Level 2
Copanlisib	60 mg	45 mg	30 mg
Ibrutinib	560 mg daily	420 mg daily	280 mg daily

*Dose reduction starts from the treating dose.

Dose escalation is allowed after the DLT period for ibrutinib to the FDA approved dose levels of 560 mg. However, patients will only be allowed to escalate to this dose once the DLT evaluation period for Dose Level 1 has passed and the dose will not exceed what has been deemed the MTD in other patients. There will be no intrapatient dose escalation of copanlisib. Once a dose reduction for copanlisib of a patient has occurred, the dose level may not be re-escalated during subsequent treatment cycles.

The sections below describe dose reduction steps for patients enrolled in the expansion phase of the study. For patients in the dose expansion phase, the dose must be held per these guidelines and these dose reduction steps can be followed after cycle 1 and per discussion with the PI. Inability to meet treatment criteria will result in holding the dose. If patients have been dose reduced to dose level -1 and continue to meet dose modification criteria to reduce the dose, they will be removed from study treatment.

Table 9-7. Dose modification guidelines			
Toxicity Category	**Severity (CTCAE 5.0 Grade)**	**Dose Modifications for ibrutinib**	**Dose Modifications for copanlisib**
HEMATOLOGIC			
Anemia	***Dose modify/hold copanlisib. May dose modify/hold ibrutinib as clinically indicated***		
	Grade ≥3 (Hgb <8 g/dL)	Investigator discretion for ibrutinib dosing	Delay copanlisib infusion until Hgb resolves to ≤ grade 3 Dose reduction by 1dose 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.
Neutropenia	***May dose modify/hold either ibrutinib, copanlisib or both as clinically indicated***		
	Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain ibrutinib dose	Maintain copanlisib dose
	Grade ≥3 (ANC < 1.0 x 10^9/L)	Delay ibrutinib dose until resolves to ≤ Grade 1, then: If resolved ≤ 7 days, then maintain dose level If resolved > 7 days, then reduce 1 dose level Growth factor support is allowed after cycle 1.	Delay copanlisib infusion until ANC resolves to < grade 3 Dose reduction by 1dose 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. Growth factor support is allowed after cycle 1.
	Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Delay ibrutinib dose until resolves to ≤ Grade 1, then reduce 1 dose level Growth factor support is allowed after cycle 1.	Delay copanlisib until febrile neutropenia resolves Dose reduction by 1dose 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. Growth factor support is allowed after cycle 1.
Thrombocytopenia	***May dose modify/hold either ibrutinib, copanlisib or both as clinically indicated***		
	Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain ibrutinib dose	Maintain copanlisib dose
	Grade 3 (PLT < 50-25 x 10^9/L)	Delay ibrutinib dose until resolves to ≤ Grade 1, then: If resolved ≤ 7 days, then maintain dose level If resolved > 7 days, then reduce 1 dose level	Delay copanlisib infusion until platelet resolves to >75k

	Grade 4 (PLT < 25 x 10^9/L)	Delay ibrutinib dose until resolves to ≤ Grade 1, then reduce 1 dose level	Dose reduction by 1dose 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.
Bleeding	***Dose modify/hold Ibrutinib because of association with hemorrhagic event. May dose modify/hold copanlisib as clinically indicated***		
	Grade 1 (mild symptoms; no intervention indicated)	Maintain ibrutinib dose	Maintain copanlisib dose
	Grade 2 bleeding (medical intervention indicated/cauterization)	Omit ibrutinib dose until resolves to ≤ Grade 1, then reduce 1 dose level ibrutinib	Delay copanlisib infusion Dose reduction by 1dose 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.
	Grade ≥ 3 hemorrhage or hemorrhage resulting in intraocular bleeding causing loss of vision, transfusion of ≥ 2 units PRBCs, and any intracranial hemorrhage	Discontinue ibrutinib	Discontinue copanlisib
RENAL	***May dose modify/hold either ibrutinib, copanlisib or both as clinically indicated***		
Creatinine elevation	Grade 1 (Cr <2 x ULN)	Maintain ibrutinib dose	Maintain copanlisib dose
	Grade 2 (Cr 2-3x ULN)	Delay ibrutinib dose until resolves to ≤ Grade 1, then: If resolved ≤ 7 days, then maintain dose level If resolved > 7 days, then reduce 1 dose level	Maintain copanlisib dose
	Grade ≥3 (Cr > 3-6 x ULN)	Discontinue ibrutinib	First occurrence: Delay copanlisib infusion until resolves to ≤ Grade 2, no change to next dose Second and Third occurrence: Delay copanlisib infusion until resolves to ≤ Grade 2, decrease byone dose level Fourth occurrence: Discontinue copanlisib *Any grade 4 occurrence: discontinue copanlisib
PULMONARY	***Dose modify/hold copanlisib because of association with pneumonitis. May dose modify/hold ibrutinib as clinically indicated***		
Pneumonitis	Grade 1		Dose delaycopanlisib while treating infection. Resume at same dose once infection resolves
	Grade 2		Dose delayuntil resolves to ≤ Grade 1. Decrease by one dose level. Second occurrence: Discontinue therapy If no symptom recovery ≤Grade 1 within 28 days CT scan with lung windows. Consider pulmonaryfunction testing includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 8 weeks (+/- 1

			week), (or as per local practice) until return to within normal limits. Consider a bronchoscopywith biopsyand / or BAL.
	Grade ≥ 3		Discontinue copanlisib
GASTROINTESTINAL	***May dose modify/hold either ibrutinib, copanlisib or both as clinically indicated***		
Bilirubin *(*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only, Bilirubin will be fractionated if elevated)*	Grade 1 (> ULN - 1.5 x ULN)	Maintain ibrutinib dose per investigator discretion	Maintain copanlisib dose level with LFTs* monitored as per protocol
	Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Dose adjustments of ibrutinib per investigator discretion	Omit dose until resolves to ≤ Grade 1, then: If resolved ≤ 7 days, then maintain dose level If resolved > 7 days, then reduce 1 dose level
	Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN		Omit dose until resolves to ≤ Grade 1, then: If resolved ≤ 7 days, then maintain dose level If resolved > 7 days, then discontinue
	Grade 4 (> 10.0 x ULN)	Discontinue ibrutinib	Discontinue copanlisib
AST/ALT Elevation *Note: confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, ob struction, liver metastasis, etc. should be excluded before dose interruption/reduction*	Grade 1 (> ULN – 3.0 x ULN)	Maintain ibrutinib dose per investigator discretion	Maintain dose level with LFTs monitored as per protocol
	Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Dose adjustments of ibrutinib per investigator discretion	Maintain dose at reduce 1 dose level of copanlisib.
	Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN		Omit dose until resolves to ≤ Grade 1, then reduce 1 dose level. If no recovery in ≤28 days discontinue copanlisib, patient off study
	Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Discontinue ibrutinib	Discontinue copanlisib
AST or ALT Elevation and concurrent bilirubin elevation	AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue ibrutinib *** All patients with ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN in the absence of cholestasis ULN must immediatelybe withdrawn from copanlisib and every attempt should be made to carry out the liver event follow-up assessments	Discontinue copanlisib
Pancreatitis	Grade 2 (enzyme elevation or radiographic findings)	Dose adjustments of ibrutinib per investigator discretion	Dose adjustments of copanlisib per investigator discretion
	Grade 3 (medical intervention indicated)	Discontinue ibrutinib	Discontinue copanlisib

<table>
<tr><td colspan="4">*** Hepatic toxicity monitoring (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkal ine phosphatase is grade 2 or higher) and GGT):
In case of any occurrence of ALT/AST, or bilirubin* increase ≥ grade 2 the liver function tests must be monitored weeklyor more frequentlyif clinicallyindicated until resolved to ≤ grade 1
In case of any occurrence of ALT/ AST, or bilirubin* increase ≥ grade 3 the liver function tests must be monitored weeklyor more frequently if clinicallyindicated until resolved to ≤ grade 1; hereafter the monitoring should be continued every other week or more frequently if clinicallyindicated until the e nd of treatment with study medication
Patients who discontinued studytreatment should be monitored weekly, including LFTs* or more frequentlyif clinicallyindicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).</td></tr>
<tr><td colspan="4">ENDOCRINE</td></tr>
<tr><td rowspan="4">Hyperglycemia</td><td colspan="3">Dose modify/hold copanlisib because of association with hyperglycemia. May dose modify/hold ibrutinib as clinically indicated</td></tr>
<tr><td>Level 1: Fasting glucose > 125 – 160 mg/dL</td><td rowspan="3">Maintain ibrutinib dose per investigator discretion</td><td>Maintain copanlisib dose level</td></tr>
<tr><td>Level 2: Fasting glucose > 160 – 250 mg/dL</td><td>Maintain copanlisib dose level.
●If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), manage as for Level 3 hyperglycemia (see below)
●If asymptomatic, maintain dose and re-check FPG within 24 hours. If level worsens or improves then follow specific level recommendations. If FPG remains at Level 2:
○Maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Level 1
○Initiate or intensifymedication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if not improvement after several days.
○Instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study
○If FPG does not resolve to ≤ Level 1 within 14 days after institution of appropriate anti-diabetic treatment reduce copanlisib by1 dose level
●Consider referral to endocrinologist for diabetic management</td></tr>
<tr><td>Level 3: > 250 - 500 mg/dL (> 13.9 - 27.8 mmol/L)</td><td>Immediatelyomit copanlisib, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If level worsens or improves then follow specific level recommendations.
If FPG remains at Level 3:</td></tr>
</table>

			●Administer intravenous hydration and intervention for electrolyte/ ketoacidosis/hyperosmolar disturbances as clinicallyappropriate ●Continue to omit copanlisib ●Monitor FPG at least twice weekly until FPG resolves to ≤ Level 1 If FPG resolves to < Level 1 in 7 days or less, then re-start copanlisib and reduce by1 dose dose level If FPG remains greater than Level 1 severity for more than 7 days, then discontinue patient from copanlisib ●Initiate or continue anti-diabetic treatment as appropriate ○instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ○consider use of oral anti-hyperglycemic therapy such as metformin ●Consider referral to endocrinologist for diabetic management
	Level 4: > 500 mg/dL (≥ 27.8 mmol/L)	Dose adjustments of ibrutinib per investigator discretion	Immediatelyomit copanlisib, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. If level improves then follow specific level recommendations. If FPG is confirmed at Level 4: ●Administer intravenous hydration and intervention for electrolyte/ ketoacidosis/hyperosmolar disturbances as clinicallyappropriate ●Discontinue patient from study ●Instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ●Consider use of oral anti-hyperglycemic therapy such as metformin ●Consider referral to endocrinologist for diabetic management For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accom panied bysigns/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine

			ketones, discontinue copanlisib and following guidance for management of Level 4 fasting plasma glucose (FPG).
CARDIAC			
Arterial hypertension	***Dose modify/hold copanlisib because of association with arterial hypertension. May dose modify/hold ibrutinib as clinically indicated***		
	Pre-dose measurements BP ≥ 150/90 mmHg	Maintain ibrutinib dose per investigator discretion	Delay copanlisib until recoveryto <150/90 mmHg Consider BP lowering medication. Dosing can proceed on the scheduled dayif after at least 2 consecutive measurements BP returns to < 150/90 mmHg. If BP doesn't return to < 150/90 mmHg, delay dosing until next visit.
	During infusion: Grade 3 (≥ 160/100 mmHg)	Dose adjustments of ibrutinib per investigator discretion	Infusion can be interrupted or slowed down and administration of BP lowering therapyshould be initiated. Infusion maybe resumed when BP has returned to < 150/90 mmHg at the investigator's discretion or skipped. Subsequent studydrug administrations maybe reduced by 1 dose level at the investigator's discretion.
	Post-dose: Drug-related Grade 3 (≥ 160/100 mmHg despite optimal anti-hypertensive treatment)	Dose adjustments of ibrutinib per investigator discretion	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 studydrug administrations maybe reduced by 1 dose level at the investigator's discretion.
	Grade 4 (Malignant hypertension, transient/permanent neurologic deficits, hypertensive crisis)	Discontinue therapy	Discontinue therapy
Left ventricular systolic dysfunction **Event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.*	***Dose modify/hold copanlisib because of association with cardiac dysfunction. May dose modify/hold ibrutinib as clinically indicated***		
	Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain ibrutinib dose per investigator discretion	Maintain copanlisib dose level, and continue with caution Repeat LVEF within 4 weeks or as clinicallyappropriate
	Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	Dose adjustments of ibrutinib per investigator discretion	- Omit copanlisib dose until resolved* (as defined to left), then reduce 1 dose level copanlisib - LVEF measurement to be repeated, if not resolved* within 28 days, permanentlydiscontinue patient from copanlisib treatment
	Refractory or poorly controlled, ejection fraction < 20%	Discontinue therapy	Discontinue therapy
QTc prolongation	***Dose modify/hold copanlisib because of association with QTc prolongation. May dose modify/hold ibrutinib as clinically indicated***		
	QTc > 500 ms (≥ Grade 3) or > 60 ms change from baselineon at least two separate ECGs	Dose adjustments of ibrutinib per investigator discretion	First Occurrence: - Omit copanlisib dose

			- Perform a repeat ECG within one hour of the first QTc of > 500 ms or >60 ms from baseline. Repeat as clinically indicated until QTcF returns to < 480 ms - Seek cardiologyinput; address electrolytes, correct with supplements as clinicallyindicated ; review concomitant medication - Once QTc prolongation has resolved, restarted at one lower dose level Second Occurrence: - Off study
Atrial fibrillation or atrial flutter	***Dose modify/hold ibrutinib because of association with atrial fibrillation. May dose modify/hold copanlisib as clinically indicated***		
	Grade 1 or 2	Maintain ibrutinib dose level	Maintain copanlisib dose level
	Grade 3 (Symptomatic and incompletelycontrolled with medications or device)	Omit ibrutinib dose until resolves to ≤ Grade 1, then resume at reduce 1 dose level Third recurrence: off study	Dose adjustments of copanlisib per investigator discretion
	Grade 4	Discontinue ibrutinib	Discontinue copanlisib
OTHER CARDIAC DISORDERS	***May dose modify/hold copanlisib, ibrutinib or both as clinically indicated***		
	Grade 1 or 2	Omit dose until resolved to ≤ Grade 1, then reduce 1 dose level	
	Grade ≥ 3	Off study	
SKIN	***May dose modify/hold copanlisib, ibrutinib, or both based on association with rash***		
Rash	Grade 1 (<10% body surface area BSA; no associated erythema or pruritus)	Maintain ibrutinib dose level Consider to initiate appropriate skin toxicitytherapy, e.g. with topical corticosteroids B.I.D. and oral antihistamines	Maintain copanlisib dose level
	Grade 2 (10 to 30% BSA and associated with erythema or pruritus; limited instrumental activities of dailyliving (ADL))	*Tolerable Grade 2:* •Initiate/intensifyappropriate skin toxicitytherapy, e.g. with topical steroids B.I.D. and oral antihistamines. •Maintain ibrutinib level. *Intolerable Grade 2 (if considered associated with ibrutinib):* •Omit ibrutinib dose and initiate/intensifyappropriate skin toxicity therapy, e.g. with topical steroids B.I.D., oral antihistamines and oral steroids. *First occurrence:* •If resolved to grade ≤ 1 in ≤ 2 weeks, maintaindose level. •If resolved grade≤ 1 in more than 2 weeks, ↓ 1 dose level.	*Tolerable Grade 2:* •Initiate/intensifyappropriate skin toxicitytherapy, e.g. with topical steroids B.I.D. and oral antihistamines. •Maintain copanlisib level. *Intolerable Grade 2 (if considered associated with copanlisib):* •First occurrence: Delay infusion until resolves to ≤ Grade 1, maintain dose level •Second and Third occurrence: Delay infusion until resolves to ≤ Grade 1, decrease by one dose level •Fourth occurrence: Discontinue •Start skin directed therapy

		•Consider continuingskintoxicitytherapyup to 2 weeks after re-introduction of ibrutinib. In case of flare after cessation of skin toxicitytherapy, consider prompt re-implementation. *Second occurrence:* Omit ibrutinib dose andfollow treatment guidance above. •Once resolved to grade ≤ 1, reduce ibrutinib 1 dose level According to the investigators discretion, a paired skin biopsycould be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.	
	Grade 3 (Non-macular, papular rash covering >30%BSA with or without symptoms)	•Initiate/intensifyappropriate skin toxicitytherapy, e.g. with topical steroids B.I.D., oral antihistamines and oral steroids. •May continue ibrutinib with short term follow up of rash to monitor for improvement •If rash does not improve after 5 days on intensified approach, then consider stopping ibrutinib. Once resolved to grade ≤ 1, consider reducing ibrutinib 1 dose level. •Consider continuing skin toxicitytherapy up to 2 weeks after re-introduction of ibrutinib. In case of flare after cessation of skin toxicity therapy, consider prompt re-implementation.	•Initiate/intensify appropriate skin toxicity therapy, e.g. with topical steroids B.I.D., oral antihistamines and oral steroids. •May proceed with copanlisib infusion with short term follow up of rash to monitor for improvement •If rash does not improve after 5 days on intensified approach, then delay infusion of copanlisib. •Consider continuing skin toxicity therapy up to 2 weeks after re-introduction of ibrutinib. In case of flare after cessation of skin toxicity therapy, consider prompt re-implementation. •First occurrence: Delay infusion until resolves to ≤ Grade 1, decrease by one dose level •Second occurrence: Delay infusion until resolves to ≤ Grade 1, decrease by one dose level •Third occurrence: Discontinue
	Grade 3 (Macules or papules covering >30%BSA with or without symptoms)	•Omit ibrutinib dose and initiate/intensifyappropriate skin toxicity therapy, e.g. with topical steroids B.I.D., oral antihistamines and oral steroids. •Once resolved to grade ≤ 1, reduce ibrutinib 1 dose level. •Consider continuing skin toxicitytherapy up to 2 weeks after re-introduction of ibrutinib. In case of flare after cessation of skin toxicity therapy, consider prompt re-implementation.	First occurrence: Delay infusion until resolves to ≤ Grade 1, decrease by one dose level Second occurrence: Delay infusion until resolves to ≤ Grade 1, decrease by one dose level Third occurrence: Discontinue

		According to the investigators discretion, a paired skin biopsycould be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.	
	Grade 4 (including other skin toxicity than maculo-papular rash)	Discontinue ibrutinib According to the investigators discretion, a paired skin biopsycould be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.	Discontinue copanlisib
GENERAL	***May dose modify/hold copanlisib, ibrutinib or both as clinically indicated***		
Fatigue	Grade 1 or 2	Maintain dose level	
	Grade 3	Omit dose until resolves to ≤ Grade 1, then: If resolved ≤ 7 days, then maintain dose level If resolved > 7 days, then reduce 1 dose level	
	Grade 4	Discontinue therapy	
OTHER NON-HEMATOLOGIC EVENTS	***May dose modify/hold copanlisib, ibrutinib or both as clinically indicated***		
	Grade 1 or 2	Maintain dose level	
	Grade 3	Omit dose If resolved ≤ 7 days, then maintain dose level If resolved > 7 days, then reduce 1 dose level	
	Grade 4	Discontinue therapy	

Note: The investigator mayremove any patient from the study for any toxicity, if investigator believes that it is in the best inte rest of the patient.

Note: The investigator maydose reduce either ibrutinib or copanlisib. In situations where toxicities are associate with one drug, the investigator must hold and reduce drug associated with toxicity. The second drug maybe continued or modified at the investigator's discretion.

Note: If any one drug is permanentlydiscontinued, the patient will be taken off study unless in exceptional situations i.e. if the patient is clearlybenefiting from the studytreatment (i.e. stable disease or better) and in the opinion of the investigator no safetyconcerns are present, the patient mayremain on the studytreatment.

9.8. Management of Toxicities or Procedures

Reproductive Toxicity

Copanlisib may cause embryo-fetal harm. Female patients of childbearing potential are advised to use highly effective contraception (contraception with a failure rate <1% per year) during and up to 1 month after treatment with copanlisib. Advise male patients with female partners of childbearing potential to use highly effective contraception in addition to a barrier method of contraception during and up to 1 month after treatment with copanlisib.

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking ibrutinib and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Women of child-bearing potential who are sexually active must use highly effective contraception during the study and for 1 month after the last dose of ibrutinib or copanlisib. Men who are sexually active must use highly effective contraception during the study and for 1 month after the last dose of ibrutinib or copanlisib. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue ibrutinib and copanlisib immediately. Pregnancy in a female subject or a male subject's partner must be reported in the same manner as a SAE. Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. For women with therapy-induced amenorrhea, oophorectomy or serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status.

Guidelines for Ibrutinib and Copanlisib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery (including excisional lymph node biopsies). The following guidance should be applied to the use of ibrutinib in the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib:

Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure.

For bone marrow biopsies that are performed while the subject is on ibrutinib or copanlisib, it is not necessary to hold ibrutinib or copanlisib for these procedures.

Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes. For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure or the discretion of the investigator.

Copanlisib may be interrupted at the discretion of the treating physician with surgical procedures.

Guidelines for Second Primary Malignancies

Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %). All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and collected for 30 days post study treatment.

Management of lymphocytosis and leukostasis associated with ibrutinib:

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood.12

Upon initiation of ibrutinib, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/MCL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks. High number of circulating malignant cells (>400,000/mcL) may confer increased risk; these patients should be closely monitored. Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression. Administer supportive care such as hydration and/or leukapheresis as indicated. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings.

Management of hematologic toxicity associated with copanlisib

Neutropenia and febrile neutropenia are listed in the current version of investigator's brochure for copanlisib as expected adverse events. Please refer to Table 9-7 for dose modifications based on hematologic toxicity. If the guidelines are not followed, the rationale for other measures is to be documented in detail in the patient's medical record.

Management of Pneumonitis in patients receiving copanlisib

Non-infectious pneumonitis has been associated with PI3K inhibitors. The investigator is requested to differentiate between non-infectious pneumonitis, 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. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".

In the event of suspected non-infectious pneumonitis, modify copanlisib treatment as per guidelines in Table 9-7 and Table 9-8. If the guidelines are not followed, the rationale for other measures is to be documented in detail in the patient's medical record.

Table 9-8. Management of Pneumonitis

Worst Grade	Recommended Investigations	Recommended Management	Action with Copanlisib	Retreatment Dose after Recovery
Grade 1	CT scans with lung windows. Repeat at least every 8 weeks (+/- 1 week), (or as per local practice) until return to within normal limits.	No specific therapy is required	No change	NA
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 8 weeks (+/- 1 week), (or as per local practice) until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Dose interruption until recovery to ≤ grade 1	Decrease dose to the next lowest dose level, minimum dose is 30mg copanlisib[a]
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 8 weeks (+/- 1 week), (or as per local practice) until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue copanlisib	NA
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 8 weeks (+/- 1 week), (or as per local practice) until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue copanlisib	NA

Guidelines for the treatment of copanlisib induced arterial hypertension

No dose 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. Otherwise dosing must be delayed.

If drug-related arterial hypertension (post-dose blood pressure of CTCAE Grade 3 or ≥ 160/100 mmHg) is not manageable with optimal antihypertensive treatment, the dose for the subsequent copanlisib administrations may be reduced by 1 or 2 dose levels at the investigator's discretion. Patients with a post-dose blood pressure that may have life-threatening consequences (e.g. malignant arterial hypertension, transient or permanent neurologic deficit, hypertensive crisis) must permanently discontinue the study drug. Please see table 9-7.

Treatment of blood pressure increases associated with copanlisib

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

The management of acute blood pressure increases following copanlisib will need to be individualized for each patient, but experience in Phase I has suggested the benefit of dihydropyridine calcium channel blockers (i.e. amlodipine, felodipine). Topical nitrates should also be considered. Verapamil and diltiazem(non-dihydropyridine calcium channel blockers and moderate inhibitors of CYP3A4) should be used with caution due to a potential CYP3A4 interaction. In general, it is advisable for sites to be prepared, so that antihypertensive medication is readily available in case of need.

In the event of the occurrence of arterial hypertension ≥ 150/90 mmHg during infusion of copanlisib at any cycle, antihypertensive treatment is suggested as indicated in Table 9-7. In the event of the occurrence of CTCAE Grade 3 arterial hypertension (≥ 160/100 mmHg) during infusion of copanlisib, the infusion should be interrupted and antihypertensive treatment as suggested above is administered. Infusion can be resumed when blood pressure has returned to <150/90 mmHg.

Guidelines for the monitoring and treatment of copanlisib induced hyperglycemia

Hyperglycemia is a common side effect of PI3K and also mTOR inhibitors. Hyperglycemia is often infusion-related and is dose-dependent. Transient increase of glucose levels have been observed in some patients. Regular monitoring of FPG to identify early hyperglycemia and prevent acute/sub-acute complications is important. Caution is warranted for patients with history of DM, or taking corticosteroids, or with other severe medical conditions (e.g. infections), or patients who show potential acute signs suchas poly-nocturia, polydipsia, confusion, etc. Hyperglycemia management guidance includes patient education and dietetic measures/life-style changes as well as appropriate anti-diabetic medications as per investigator's decision and/or local guidelines.

Oral anti-diabetics such as metformin should be considered for sustained and more severe hyperglycemia (other drugs as appropriate). Provided hyperglycemia is asymptomatic and there are no acute complications, sufficient time should be given to install optimal management (e.g. up titrate metformin, addition of a second oral anti-diabetic agent to be considered as needed, etc.). Patients with history of DM, management should take prior anti-DM treatments into account. Note that some oral anti-diabetic are CYP3A inducers or inhibitors and may be prohibited (see Appendix 1 for more details). Patients who develop Grade 3 or 4 or symptomatic hyperglycemia should be managed urgently as per standard clinical practice, with the goal of stabilizing glycemic control within 24 hours. More guidance on dose reductions and interruptions is provided in Table 9-7.

Recommendations on meal timing on infusion days

Caloric intake and timing recommendations for diabetic patients 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.

Cycle 1 Day 1

Fasting is required before the first glucose measurement on date of infusion.

Subsequent dosing beyond Cycle 1 Day 1:

Fasting is not required before the first glucose measurement.

Management of transient post-infusion glucose increases that can occur with copanlisib study treatment

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially.

Table 9-9. Hyperglycemic management during copanlisib infusion

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

Table 9-10. Hyperglycemic management in between copanlisib infusion		
Criteria	**Recommendation**	**Suggested Treatment**
Max post infusion glucose > 200 mg/dL noted on subsequent days	• Oral Glucose Lowering Medication Recommended at physicians' discretion on subsequent days • **Consultation with endocrinologist is recommended.**	• The use of sulphonylurea/metaglinides, insulin secretagogues medications to manage increased glucose levels post drug infusions is not recommended. • Treatment with glucose lowering medication suggested according the local standards of practice. • Based on mechanisms of action and decreased risk of hypoglycemia, metformin, SGLT-2-inhibitor or DPP4-inhibitor might be useful treatment options
• DPP4 = Dipeptidyl peptidase-4; IV = intravenous; SGLT-2 = Sodium/glucose co-transporter 2		

Guidelines for the Management of Ibrutinib and Copanlisib induced stomatitis/oral mucositis

General guidance and management include patient awareness and early intervention.

Evaluation for herpes virus or fungal infection should be considered.

Patients should be informed about the possibility of developing mouth ulcers/ oral mucositis and instructed to report promptly any signs or symptoms to their physician, Patients should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®), or as per local practice.
- Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with copanlisib metabolism.

Guidelines for management of hyperlipidemia

Total cholesterol, LDL and triglycerides will be tested only at with fasting labs on Cycle 1 Day 1 and non-fasting labs on Day 1 of every even cycle starting from Cycle 2, and at the EOT visit. If lipids are abnormal with non-fasting labs, a repeat fasting lipid panel is recommended. As lipids are monitored for the duration of this study it is recommended to treat significant deviations from normal range with standard interventions and therapy in standard doses according to local medical practice. Goals of therapy are to keep fasting triglycerides < 300 mg/dL and low-density lipoproteins (LDL) < 190 mg/dL (lower LDL depending on cardiovascular risk) in patients with a life expectancy >1 year. The goals for fasting triglycerides can be raised to < 500 mg/dL for patients with life expectancy <1 year. Although there is a paucity of data on the effects of hyperlipidemia and cancer outcomes, these goals have been chosen to decrease risk of established complications of hypertriglyceridemia (pancreatitis) and hypercholesterolemia (cardiovascular events).

Guidelines for the treatment of copanlisib or ibrutinib induced diarrhea

The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Concomitant medication for the treatment of diarrhea should be considered, as per local practice and best investigator's judgment and may consist for example, as per "the recommended guidelines for the treatment of cancer treatment-induced diarrhea"[38], of loperamide given at a standard dose (e.g. initial administration of 4mg, then 2mg every 4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures could be considered for Grade 1-2 diarrhea. More severe diarrhea should be treated appropriately according to investigator discretion, including for example IV fluids.

Dose modification of copanlisib or ibrutinib in case of treatment related diarrhea should follow the guidelines presented above for other non-hematological adverse events.

Guidelines for the treatment of ibrutinib or copanlisib induced skin toxicity

Skin toxicity is a class-effect observed with both ibrutinib and PI3Ki/mTORi agents. Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as adverse event. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate co-medication and treatment interruption if needed. Photographs of a skin rash event as well as skin biopsy are recommended, if possible. According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) to further assess rash if clinically appropriate.

Recommended therapies for skin toxicity events:

- Topical steroids of moderate potency (face and folds): triamcinolone 0.025%; clometasone 0.05% (< 8 weeks continuously), for mild and moderate rashes.
- Topical steroids of high potency (trunk/extremities): fluocinonide 0.05%; clobetasol 0.05% cream or spray (< 8 weeks continuously), for mild and moderate rashes.
- Oral antihistamines (sedating, evening): diphenhydramine 25 to 50mg t.i.d; hydroxizine 25mg tid or q.i.d;
- Oral antihistamines (non-sedating, day time): fexofenadine 180mg q.d. or 60mg tid (monitor the use of this class of drugs since skin toxicity has also been reported)
- Oral corticosteroids: prednisone 0.5mg/kg or equivalent up to 2 weeks of treatment
- In caseof mild acneiform rashes topical antibiotics: clindamycin 1% to 2%; erythromycin 1% to 2% (gel or solution formulation can be used, ointments cannot be used); metronidazole 1%; silver sulphadiazine.
- For more severe acneiform rashes oral antibiotics: doxycycline 100mg B.I.D.; minocycline 100mg B.I.D.; oxytetracycline 500mg B.I.D. for 6 weeks can be considered. If infection suspected (yellow crusts, purulent discharge, painful skin/nares), then switch to broad spectrum/gram negative antibiotics; consider skin swab for bacterial culture.
- Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
- For severe pruritus GABA Agonists: Gabapentin 300mg every 8 hours, or pregabalin 50 to 75 mg every 8 hours (to adjust of renal impairment) can be considered. Dose should be adjusted depending on patient's clinical condition beware of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others AEs.

Dry skin has been reported, it is recommended that patients with dry skin use mild and fragrance free soaps and detergents. According to the severity and BSA extension patients may apply mild moisturizers, ammonium lactate cream 12% or salicylic acid cream 6% B.I.D.

Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including regular use of sunscreen (factor 20 at least), wearing of sunglasses, using of hats, and protective clothes when outdoors.

Guidelines for the management of ibrutinib induced hemorrhage

Fatal bleeding events have occurred in patients treated with ibrutinib. Bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib. The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post- surgery depending upon the type of surgery and the risk of bleeding. If bleeding diathesis occurs, consider platelet transfusions to reverse the inhibition of platelet adhesion and collagen induced platelet aggregation from ibrutinib[39].

Guidelines for the infectious prophylaxis

Cytomegalovirus (CMV) reactivation and Pneumocystis pneumonia (PCP) have been observed in patients treated with other PI3K inhibitors suchas idelalisib. Patients will undergo CMV PCR testing every cycle. Patients should be placed on prophylaxis for PCP pneumonia unless there is a medical contraindication.

9.9. Criteria to Resume Treatment after Complete Response:

For subjects who stop copanlisib after achieving a complete response, copanlisib may be restarted upon radiographic and pathologic progression of disease. Subjects may resume treatment if any drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 or 4 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

Patients must also meet the following criteria:

- Investigator assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Repeat treatment with copanlisib and ibrutinib will not delay an imminent intervention to prevent serious complications of disease progression (eg CNS metastasis)
- Participant provides written informed consent prior to receiving additional copanlisib and ibrutinib.

A radiographic assessment with FDG-PET/CT or PET-MRI should be performed within 6-10 weeks of re-initiating treatment to assess response.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1. General requirements

Evaluations during this period are per Table 10-1.

10.2. Treatment period

Patients will receive study treatments copanlisib and ibrutinib until disease progression, unacceptable toxicity or until other discontinuation criteria are met, whichever come first. Maximum duration of treatment is 36 cycles not exceeding 36 months.

Patients will follow the visit schedule as per Table 10-1. Permitted visit windows for assessments within the treatment period and at efficacy follow-up visits are included in the table. If copanlisib is held based on achievement of a complete response, patient visits will be every 2 cycles during C1-C6, every 3 cycles during C7-C12, every 4 cycles during C13-36.

Information on drug exposure will be collected on the Dosage Administration Record eCRF. Concomitant medications/significant non-drug therapies prior to start (≤ 28 days) and after start of study treatment will be recorded on the appropriate eCRFs.

Compliance will be assessed by the investigator and/or study personnel at each visit using box counts and information provided by the caregiver.

10.3. End of treatment visit including premature withdrawal and study safety followup

Patients will continue study treatment until disease progression, until any of the study's discontinuation criteria are met, or a maximum treatment period of 36 cycles, not exceeding 36 months (Section 13). Patients who discontinue study treatment or at completion therapy should be scheduled for an End-of-Treatment visit within 7 days from treatment discontinuation or as early as possible per patient's convenience at which time all of the assessments listed for the EOT visit will be performed. For details of assessments, refer to Table 10-1. An End of Treatment eCRF page should be completed, giving the date and reason for discontinuation of study treatment. Patients will have an additional follow up 1 month after last dose.

If a patient withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment eCRF page.

Patients will be assessed for any adverse events 30 days, +/- 7 days, from the last dose of either study drug or until new therapy is initiated, whichever comes first.

10.4. Correlative studies

Patients consented on this trial will have tumor samples analyzed for genomic alterations via next generation targeted sequencing. Optional post treatment biopsy will be obtained to compare the differences in genomic alterations prior to treatment and post treatment. In addition, circulating tumor DNA and circulating tumor RNA samples will be collected throughout treatment to serially assess the genomic profile of treated patients.

Gene sequencing will be performed in the CLIA certified Molecular Diagnostics Service laboratory, a division of the MSKCC Pathology Department, using IMPACT-Heme (Integrated Mutation Profiling for Actionable Cancer Targets Hematology Panel) with paired tumor and normal tissue samples, or a custom panel of genes depending on baseline IMPACT-Heme results. IMPACT provides full exon coverage of 410 cancer related genes including CARD11, MYD88, PIK3CA, BTK, and can be used to detect base substitutions, small indels, copy number alterations and select gene re-arrangements. In some cases, the Molecular Diagnostic Service will utilize an additional assay, such as Sanger Sequencing, B cell clonality, or fluorescence in situ hybridization (FISH), to confirm specific results from these multiplexed assays. We will assess for the following:

1) Determine variations on circulating tumor RNA throughout treatment
2) Correlate spectrum of genomic mutations in tumor tissue versus circulating tumor DNA
3) Assess tumor variant allele frequency in circulating tumor DNA
4) Correlate circulating tumor DNA to radiographic response

Table 10-1. Schedule of Evaluation										
Timepoint	Screening		C1D1	C1D8	C1D15	CxD1	CXD8	CXD15	EOT	30 day FU after last dose[H]
Window	-28	-7		+/- 3 days	+/- 3 days	+/-3 days	+/-3 days	+/-3 days	+/- 7 days	+/- 7 days
Treatment										
Copanlisib			X	X	X	X[A]	X[A]	X[A]		
Ibrutinib			Daily							
Evaluation										
Obtain Informed Consent	X									
Demography	X									
Inclusion/Exclusion criteria	X									
Medical/Diagnosis/Treatment history	X									
Prior/Concomitant medications	X		X	X	X	X				X[K]
Physical Examination	X		X	X	X	X			X	X
ECOG and Vitals (Weight, Blood pressure, Pulse, Resp, Temp)	X		X	X	X	X			X	
Hematology: CBC with Diff		X	X	X	X	X			X	
Chemistry(BMP, TBili, AST, ALT, TP, Alb, AP, UA, LDH, amylase, lipase, GFR, Mag, Phos)		X	X Fasting	X	X	X	X	X	X	
Lipid panel Urinalysis, Urine protein		X				Day 1 Cycle 3, 5, 7, 10, 13, 17, 21, 25, 29, 33			X	
T3, T4, TSH		X				As clinicallyindicated			X	
Fructosamine		X			X	X			X	
Hemoglobin A1c		X				X			X	
Coagulation (PT/PTT)		X							X	
B cell Clonalityby NGS			X			Day 1 Cycle 3, 5, 7, 10, 13, 17, 21, 25, 29, 33			X	
Hepatitis B/C[B]	X		Hepatotoxicity testing/procedures as clinicallyindicated[C]							
HIV	X									
Cytomegalovirus PCR	X					X			X	
Serum/Urine beta-HCG for women of childbearing age		X								
Post Infusion Glucose Evaluation[D]			X[D] Fasting	X[D]	X[D]	X[D]	X[D]	X[D]		
Post Infusion Blood Pressure[E]			X[E]	X[E]	X[E]	X[E]	X[E]	X[E]		
Radiographic assessment[F]	X					Before Day 1 Cycle 3, 5, 7 (first 6 months), 10, 13, (1 year), 17, 21, 25, 31 (year 2-3)			X (if not within 4 weeks)	
ECHO or MUGA	X								X	
ECG	X								X	

PCP pneumonia prophylaxis			Continuous (unless clinicallycontraindicated)							
Pill Diary			X			X			X	
Tumor biopsy(archived/fresh biopsy)[G]	X[G]								Optional[G]	
Research Blood Tests: ctDNA, ctRNA			X	X	X	Cycle 2: D1, D8, D15 Cycle 3-7: D1			X	
Research Blood Tests: Pharmacokinetics[J]					X					

A: Copanlisib Dosing: If copanlisib is held based on achievement of a complete response, patient visits will be every 2 cycles during C1-C6, every 3 cycles during C7-C12, every 4 cycles during C13-36.

B: Hepatitis Evaluation: HbsAg, HBcAb, anti-HCV Ab, Hep B/C PCR if positive

C: Additional viral hepatitis workup as clinicallywarranted: HAAb, HBsAg, HBsAb, HBcAb, HCV RNA or HDV RNA (where needed), H EAb, CMVAb, EBcAb, CMV IgM Ab, EBV IgM Ab, HSV, AP, CPK, LDH,Carriers of hepatitis B should be closelymonitored for clinical and laboratorysigns of active HBV infection, signs of hepatitis during and for several months following ibrutinib/copalisib treatment. Carriers of hepatitis B (positive HBsAg and/or HBcAg but negative HBV-DNA is required to be on prophylactic antiviral therapy. If viral load becomes positive, patients should be withdrawn from study. Hep C carriers (anti-HCV Ab positive, negative HCV-RNA PCR must be tested monthlyfor HCV reactivation. If HCV-RNA PCR becomes positive, patients should be withdrawn from study.

D: Post Infusion Glucose Evaluation: C1D1 – fasting glucose prior to copablisib (0h), 60 min (end of infusion) and 2 hours; all subsequent doses – non-fasting glucose prior to copanlisib (0h), post infusion.

E: Post Infusion Blood Pressure Evaluation: Blood pressure (5-10min, +/- 10 min) prior to copanlisib must be <150/90mmHg for two consecutive measurements. If blood pressure prior to infusion is ≥150/90 mmHg, medical intervention or dose delayshould be considered. Blood pressure post infusion should b e measured at 30 min (mid-infusion), 60 min (end of infusion), 1 hour and 2 hour post infusion (+/- 10 min).

F: Radiographic assessment via PET and CT chest/abdomen/pelvis and neck CT if clinicallyindicated (MRI will be used for those who are unable to undergo CT scans).

G: Pretreatment archived biopsymaterial (10-15 x 10 microns) or an optional pretreatment core biopsy (2-3 cores). Post treatment optional core biopsy(2-3 cores).

H: Maximum 36 cycles, not exceeding 36 months of treatment

J: Exact schedule for PK testing is in Table 9-4.

K: Not required to collect if patient has begun new anti-cancer therapywithin 30 days after last dose of either study drug on protocol.

11.0 TOXICITIES/SIDE EFFECTS

11.1. Adverse Event

11.1.1. Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g. hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in Medidata. Conditions that were already present at the time of informed consent should be recorded in the Medical History in Medidata. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment or until initiation of new therapy, whichever comes first. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 11.2.1

- All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded in Medidata.
- Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.
- Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (Cheson criteria), should not be reported as a serious adverse event.
- Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

11.1.2. Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded in Medidata. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

11.2. Serious Adverse Event

A serious adverse event is one that is fatal or life-threatening (see below), is temporarily or permanently disabling, requires inpatient hospitalization (initial or prolonged), or is associated with a congenital anomaly, a new cancer or a drug overdose (either accidental or intentional). In addition, any event suggesting a significant hazard, contraindication, side effect or precaution should also be considered serious.

11.3. Life-threatening event

The event is an immediate risk of death from the reaction as it occurred. Life-threatening does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

11.4. Reporting procedures for adverse events

All adverse events occurring during the study, observed by the investigator or reported by the subject, will be reported to the IRB either in memorandum form or on the Medidatatoxicity form. The following attributes must be assigned: description; dates of onset and resolution; severity; assessment of relatedness to study drug, other suspect drug, or device; and action taken. The investigator may be asked to provide follow-up information.

11.5. Ibrutinib anticipated toxicities

Ibrutinib is an FDA approved drug for mantle cell lymphoma.

Likely (>20%): Diarrhea, nausea, constipation, abdominal pain, vomiting, upper respiratory tract infection, fatigue, peripheral edema, bruising, rash, musculoskeletal pain, dyspnea, decreased appetite, platelets decreased, neutrophils decreased, hemoglobin decreased

Less Likely (4-20%): stomatitis, dyspepsia, urinary tract infection, pneumonia, skim infections, sinusitis, pyrexia, asthenia, petechiae, muscle spams, arthralgia, cough, epistaxis, dehydration, dizziness, headache, hyperuricemia, hemorrhage (gastrointestinal bleeding, hematuria and post procedural hemorrhage), hypertension, second primary malignancies- most common non-melanoma skin cancer

Rarely (<3%): intracranial and subdural hematoma, cardiac arrhythmias, lymphocytosis, tumor lysis syndrome, progressive multifocal leukoencephalopathy

Most side effects listed above have been mild to moderate in severity; however severe side effects have occurred. Some side effects have been severe enough to lead to study drug discontinuation, dose modification or reduction, hospitalization, disability and sometimes death.

11.6. Ibrutinib adverse events of special interest

<u>Hemorrhagic Adverse Events</u>

Fatal bleeding events have occurred in patients treated with ibrutinib Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib. The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Subjects in the current study will be monitored closely for hemorrhagic adverse events. Ibrutinib should be held at least 3 to7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding (please refer to Section 9.7 for further details).

<u>Infection</u>

Fatal and non-fatal infections have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Monitor patients for fever and infections and evaluate promptly.

<u>Cytopenias</u>

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with ibrutinib. Monitor complete blood counts monthly.

Atrial Fibrillation

Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of ibrutinib treatment and dose modification based on recommendations in Section 9.

Hypertension

Hypertension (range, 6 to 17%) has occurred in patients treated with ibrutinib with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Secondary Primary Malignancies

Other malignancies (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Assess the baseline risk (e.g. high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. Advise women to avoid becoming pregnant while taking ibrutinib and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

11.7. Copanlisib anticipated toxicities

The side effects listed below have been reported by patients who have received copanlisib in clinical trials

Likely (>20%): Anemia, hyperglycemia, hypertension, fatigue, nausea, diarrhea, neutropenia (including febrile neutropenia), infections, rash (including macular, maculopapular, pruritic, pustular, erythematous, generalized, exfoliative rash, pruritus/Pruritus generalized, dermatitis acneiform, dermatitis allergic and dermatitis exfoliative)

Less Likely (4-20%): Dysgeusia, leukopenia, lymphopenia, elevated amylase and lipase increased, hypomagnesemia, hyponatremia, paraesthesia, pneumonitis, interstitial lung disease, thrombocytopenia, vomiting, chills, mucosal inflammation (including stomatitis and mouth ulceration), dry mouth, muscle spasms

Rarely (<3%): alopecia, hyperinsulinemia, infusion related reaction, hypersensitivity, gastritis, colitis, aphthous ulcer, eosinophilia, Pancreatitis, Stevens-Johnson syndrome

Most side effects listed above have been mild to moderate in severity; however severe side effects have occurred. Some side effects have been severe enough to lead to study drug discontinuation, dose modification or reduction, hospitalization, disability and sometimes death.

11.8. Copanlisib adverse events of special interest

Non-Infectious Pneumonitis

Non-infectious pneumonitis is an adverse event of special interest. In general, non-infectious pneumonitis was symptomatic, with fever, cough, and dyspnea but asymptomatic in some patients. Therefore CT scans may be used to assess for radiographic indications of non-infectious pneumonitis. The CT findings in case of non-infectious pneumonitis were diffuse ground-glass opacities. A bronchoscopy may not show any findings. Non-infectious pneumonitis resolved in all 9 patients, usually within 2 to 4 weeks. No patient died due to non-infectious pneumonitis. In all 9 patients, study drug was interrupted and in 3 patients permanently discontinued due to non-infectious pneumonitis. Interruption of study drug alone improved non-infectious pneumonitis in 1 patient, 1 patient received steroids only, 2 patients received antibiotics only, and 6 patients received antibiotics and steroids. Re-treatment with study drugs was performed in 2 patients, resulting in re-occurrence of non-infectious pneumonitis in 1 of them.

Hyperglycemia

The PI3K/AKT pathway plays a significant role in regulating glucose metabolism. Hyperglycemia is considered as an “on target” effect of copanlisib, and has been commonlyobserved in patients treated with copanlisib with an incidence approximately 50-70%.

Hypertension

Approximately 42% of patients have post infusion drug related Grade 3 hypertension. There were no cases of Grade 4 hypertension. There was a CTC Grade 3 SAE hypertension. Hypertension was reported in the medical history of 22 out of 76 patients; 16 of them were already receiving antihypertensive treatment at study start. Antihypertensive treatment was administered in 8 treatment naive patients as a consequence of post infusion hypertension, and in 7 patients due to a worsening of already therapy controlled baseline hypertension. Six of the eight naive patients received treatment only on the day of infusion, and 2 naive patients started chronic antihypertensive treatment.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression of disease will be evaluated in this study using the RECIL criteria[37]. Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 10-1, based on physical examination, radiological evaluation and core bone marrow biopsy (in patients

with pre-existing bone marrow involvement). Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule from baseline.

Measurability of lesion for objective response and measurement of target lesions: Measurable disease: lesions that can be accurately measured in two dimensions by CT, MRI, plain x-ray of other conventional technique and have a greatest transverse diameter of 1.5 cm or greater. Non-measurable disease: All other lesions including uni dimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed by CT, or disease documented only by indirect evidence (e.g. lab values).

Assessment of tumor burden in lymphoma clinical trials can use the sum of longest diameters (SLD). In patients with disseminated disease, a maximum of three target lesions should be selected and used to estimate tumor response. Target lesions should be selected from those with the largest size that can be reproducibly measured and preferably representing multiple sites and/organs. In most cases, lymph nodes can be considered target lesions if the lymph node longest diameter measures ≥15 mm. Similar to RECIST 1.1, a lymph node measuring between 10 and 14 mm is considered abnormal but should not be selected as a target lesion. Lymph nodes measuring <10mm in diameter are considered normal. In certain anatomical sites (inguinal, axillary, and portocaval), normal lymph nodes may exist in a narrow, elongated form, and such nodes should not be selected as target lesions if alternatives are available. Extranodal lesions are selected as target lesions if they have soft tissue component, based on their size, and the ease of reproducibility of repeated measurements, with a minimum measurement of the longest diameter of ≥ 15 mm. All other lesions should be identified as nontarget lesions and should be recorded at baseline, without the need to measure them. Nontarget lesions should be followed and reported as present, absent, or clear progression.

Objective disease response assessment: Objective status is to be recorded at each evaluation according to the RECIL criteria

Table 12-1. Criteria for RECIL Response Assessment of Non-Hodgkin Lymphoma

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may voluntarily withdraw from the study or be removed from the study at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Disease progression. However, if progression develops after CR while patient is on ibrutinib alone, patients could restart treatment upon radiographic and pathologic expression of disease.
- Ineligibility (at the pretreatment evaluation) of the patient as defined in the inclusion/ exclusion criteria
- Treatment will be discontinued at the request of the patient, refusal of therapy, non-compliance, or upon the development of an intercurrent significant medical illness.
- Significant protocol violation
- Unacceptable toxicity
    - Grade 4 arterial hypertension
    - Grade 4 dermatologic toxicity
    - Non-infectious pneumonitis
    - Drug induced clinically relevant pancreatitis
    - Grade ≥3 hypersensitivity reaction
- Decision by the investigator that termination is in the patient's best medical interest.
- Loss to follow-up

- Development of active HBV or HCV infection, hepatitis, or HIV infection
- Pregnancy or a positive pregnancy test
- Death of the patient

In addition to the general study treatment withdrawal criteria, the following study specific criteria will also require premature study treatment discontinuation:

- Use of prohibited medication
- Start of any other anti-neoplastic therapy

If a study treatment withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from study treatment and record this information on the End of Treatment CRF page.

14.0 BIOSTATISTICS

14.1. Phase I

In the Phase I part the standard 3+3 dose escalation scheme will be used. If none of the initial cohort of 3 has a DLT (defined in Section 9.2) the dose level will be escalated. If one has a DLT that dose level will be expanded with 3 more patients. Dose escalation will stop if 2 or more DLTs are seen at a dose level within the treatment and observation periods as described in Section 9.2. The MTD is defined as the highest dose level at which at most 1 of the 6 patients treated at that level has a DLT. Two dose levels plus a "-1" dose level are planned for this study. The maximum sample size is 18 patients. Toxicity seen after 4 weeks that are likely or definitely related to treatment with study drugs will be collected and evaluated by the investigators.

All patients that stop protocol therapy or have dose reductions due to a DLT will be included in the DLT analysis. If a patient stopped therapy for other reasons and has taken ≤75% of planned doses (2 of 3 copanlisib doses and 21 of 28 doses of ibrutinib) in the first cycle then they will be excluded from DLT analysis. In the event that a patient withdraws from the trial due to a reason unrelated to a DLT before completing cycle one, they will be replaced. We expect that less than 10% of patients will be replaced due to insufficient time of treatment. The probability of dose escalation based on various underlying DLT rates (Table 2).

Table 14-1. DLT probability table

True DLT rate	5%	10%	15%	20%	25%	30%	40%	50%
Probability of escalation	0.97	0.91	0.81	0.71	0.60	0.49	0.31	0.17

It is expected that 2-3 patients will be enrolled per month and so the phase I portion of the trial will be completed in approximately 6 months.

14.2. Phase II

The primary objective for this phase II cohort is to assess the complete response rate based on best response by 6 months of ibrutinib and copanlisib and the secondary objective is to measure the disease control rate (stable disease, partial response, and complete response), overall response rate (partial and complete response), duration of response, progression and event free survival. A Simon mini-max two stage design will be used with the goal to increase by complete response rate based on best response by 6 months from 20% to 40%. In first stage, if 5 or more of 18 patients have responses, then the trial will proceed to stage 2. In stage 2, additional patients are enrolled to make the total sample size 33. If 11 or more responses are observed, then the combination is deemed promising. Accrual will not be held while the initial 18 patients in the first stage are evaluated for the 6-month response endpoint. The one sided type I error rate is 0.05 and the power is 0.80. A total of 33 patients will be enrolled, though patients treated at MTD/RP2D from phase I portion of the study will be included in the phase II analysis. Expected accrual is 2-3 patients per month and so the phase II portion will be completed within a year.

For other secondary objectives, the event free survival and progression free survival rates will be assessed by the Kaplan-Meier estimation. Event free survival is defined from the date of first dose to progression, or death, and any events including treatment discontinuation for adverse events or severe adverse events whichever came first. Progression free survival is defined from the date of first dose to progression or death, whichever came first. The duration of response will also be assessed by Kaplan-Meier method but on a sub-cohort of patients who showed any response.

To protect patients from excessive toxicity of the treatment during the entire treatment period, several stopping rules are implemented during the study based on the maximum total number of treated patients in both phase I and II (45).**Treatment related Grade ≥3 Pneumonitis or Colitis:** 10% unacceptable rate, 2.5% acceptable rate. Trial to hold enrollment if ≥4 deaths related to treatment at any point during the study. Otherwise, hold enrollment based on number of treated patients.

Number of treated patients	1	14	33	45
Number of Gr≥3 Pneumonitis/Colitis to stop the trial	1	2	3	4

Operating characteristics of the early stopping rule for grade ≥3 treatment related pneumonitis/colitis:

True tox rate	0.025	0.04	0.055	0.07	0.085	0.1
Probability of claiming treatment too toxic	0.092	0.224	0.377	0.528	0.661	0.767

Treatment related death: 10% unacceptable rate, 2.5% acceptable rate. Trial to hold enrollment if ≥4 deaths related to treatment at any point during the study. Otherwise, hold enrollment based on number of treated patients.

Number of treated patients	1	14	33	45
Number of death to stop the trial	1	2	3	4

Operating characteristics of the early stopping rule for treatment related death:

True tox rate	0.025	0.04	0.055	0.07	0.085	0.1
Probability of claiming treatment too toxic	0.092	0.201	0.323	0.444	0.555	0.652

Any one Grade ≥3 Treatment non-hematologic Related Toxicity: 60% unacceptable rate, 40% acceptable rate. Trial to hold enrollment if ≥25 single toxicity event related to treatment at any point during the study. Otherwise, hold enrollment based on number of treated patients.

Number of treated patients	Number of Gr>=3 non-hematologic toxicity events to stop the trial
1	1
2	2
4	4
5	5
7	6
9	7
10	8
12	9
14	10
16	11
18	12
20	13
22	14
24	15
26	16
28	17
30	18
32	19
34	20
36	21
39	22
41	23
43	24
45	25

Operating characteristics of the early stopping rule for grade ≥3 treatment non-hematologic related toxicity:

True tox rate	0.40	0.44	0.48	0.52	0.56	0.60
Probability of claiming treatment too toxic	0.099	0.194	0.339	0.522	0.707	0.854

14.3 Treatment re-initiation

Patients who discontinue copanlisib may restart if they meet requirements set out in Section 9.9 and after discussion with study PI. Patients who have a complete response, then restart copanlisib for progression will be counted as a progression. Future responses will be censored.

14.4 Exploratory assessments

Baseline targeted sequencing of patient tumor samples will be analyzed by Fisher's exact test for correlation with response/resistance and log rank test for correlation with duration of response. The proportion of patients with detectable ctDNA will be estimated along with a 95% CI as well as a mean (variance) of ctDNA. I plan to plot the variant allele frequency of each mutation over time for each patient. ctDNA levels will be correlated with response or duration of response to treatment. A multivariate logistic regression model will be fit with best response to treatment as the outcome variable and ctDNA and patient-related factors as covariates. To test the relation between ctDNA and disease status, defined as no evidence of radiographic disease (CR) vs radiographic disease (combined PR, SD, POD), all serial measurements will be used in a logit model with generalized estimating equations to correct for within-patient correlations. Logistic regression will be used to assess the correlations between the markers and tumor status. Overall survival (OS) and progression-free survival (PFS) will be assessed by Kaplan-Meier methods. The effect of ctDNA on OS will be analyzed as a time-dependent covariate using a Cox proportional hazards model. Similar evaluations will be performed on ctRNA. The statistical analysis will be primarily descriptive and the data will provide initial information regarding the kinetics of response and sensitivity of the assay itself.

Pharmacokinetic assessments will be based on patients in the phase I dose escalation level 1 and 2 cohorts. A non-compartmental analysis (NCA) will be performed in this study and pharmacokinetic parameters will be calculated using WinNonlin, in the latest version. Based on the plasma concentration–time data, the following pharmacokinetic parameters will be calculated.

	Copanlisib	Ibrutinib
Main PK parameters	Cycle 1 Day 15 Cmax, AUC(0–24)	Cycle 1 Day 15 Cmax, AUC(0–tlast), AUC(0–24) and AUC
Additional PK parameters	M-1, if applicable Cmax, AUC(0–tlast)	tmax, tlast, t1/2 CL and Vd if possible

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

NA

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory

monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Medidata) at Memorial Sloan Kettering Cancer Center. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Registration reports will be generated on an ongoing basis to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

http://cancertrials.nci.nih.gov/researchers/dsm/index.html.

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Potential risks to human subjects include drug related toxicity; pain and discomfort associated with therapy; treatment side effects; phlebotomy; and possible psychologic discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan, PET scan).

The side effects and potential toxicities of all agents are listed in sections 5.0 and 11.0. All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

If an adverse medical event occurs, the patient will first contact the primary oncologist or the principal investigator. At nights and weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the Urgent Care Center at Memorial Hospital (or to their local emergency room) to be seen.

Costs to the patient (third party insurer) will include the cost of blood tests and diagnostic studies, office visits, and those admissions which may be required as a consequence of treatment-related complications.

All serious adverse events incurred while a patient is on study will be reported to the IRB at Memorial Hospital, and Bayer. All serious adverse experiences and relevant laboratory findings will be reported to the principal investigator immediately. An adverse experience is considered serious if death occurs, the condition is life threatening, hospitalization is required, or there is permanent disability or incapacity. All information regarding serious adverse experiences must be recorded on the form provided. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

All life threatening and lethal known, unknown, or suspected reactions (toxicities) must be reported to the principal investigator. An SAE report will be submitted to Bayer within 24 hours of the principal investigator's knowledge of the event, and the IRB within 5 days. Any death, regardless of cause, must be reported to the principal investigator by telephone or fax and in writing. It is the treating physician's responsibility to investigate and report the date and cause of death of any patient entered on this trial.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- Development of a new malignancy
- Pregnancy
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening tet or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form • If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1

Bayer specific SAE reporting:

Research team shall immediately, within 24 hours at the latest, report to Bayer by e-mail to drugsafety.gpv.us@bayer.com :

- All Serious Adverse Events occurring after start of administration of BAYER product, independent of their causal relationship to study drugs
- Any other relevant safety information including but not limited to:
    - Reports of drug exposure via mother / father with and without adverse events (exposure during conception, pregnancy, childbirth and breastfeeding) including their outcome;
    - If linked to a serious adverse event, reports of misuse, abuse, overdose, medication error and other uses outside what is foreseen in the protocol, drug dependency, occupational exposure suspected transmission of an infectious agent, withdrawal syndrome, drug interactions with respect to study drugs
    - Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:
        - Development Safety Update Reports / relevant parts of IND reports for the study drugs
        - Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees (e.g., reportable non-serious cases)

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

APPENDIX 1: A list of CYP3A4 inhibitors and inducers

A list of strong inhibitors and inducers of CYP3A4 is shown below:

Strong CYP3A4 inhibitors	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, atazanavir, tipranavir, troleoandomycin, elvitegravir, danoprevir, conivaptan, boceprevir, suboxone and cobicistat
Strong CYP3A4 inducers	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum) and enzalutamide

CYP3A4 = Cytochrome P450 isoenzyme 3A4

- A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold
- Strong Inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by ≥ 80%

Source: 1-4

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