PILOT PHASE II MULTICENTER STUDY OF THE PI3K INHIBITOR COPANLISIB IN COMBINATION WITH A KETOGENIC DIET IN THE TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA OR ENDOMETRIAL CANCER

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PROTOCOL SYNOPSIS

Study Design: This is a multi-institution, open label, pilot phase II study of the PI3K inhibitor copanlisib in combination with a ketogenic diet in the treatment of patients with one of the following malignancies: (a) relapsed or refractory (R/R) follicular lymphoma (FL), (b) R/R endometrial cancer (EC) with a documented activating mutation in PIK3CA or loss of PTEN. The FL arm will enroll 23 subjects and the EC arm will enroll 19 subjects. The study will be stopped if the safety trigger is activated at the pre-specified times of interim safety analysis upon enrollment of 12 and 24 patients.

The two arms will enroll patients in parallel and independently. Safety analysis will be done by pooling patients from the two arms together. Efficacy analysis will be conducted independently within each arm.

Objectives:

Primary Objectives

- Determine the objective response rate (ORR) (complete response [CR] + partial response [PR]) in FL.
- Determine the ORR in EC.

Secondary Objectives:

- Determine the CR and PR rates in FL upon completion of the study protocol.
- Determine the CR and PR rates in EC upon completion of the study protocol.
- Determine the ORR in FL and EC at the Simon stage I analysis
- Determine patient compliance with the ketogenic diet.

Exploratory Objectives:

- Determine the PD markers including *blood* levels of insulin, c-Peptide, BHB (beta-hydroxybutyrate), triglyceride, and glucose, and urine ketones.
- Determine the PD markers including levels of pINSR, INSR, pAKT, AKT, pS6, S6, Ki-67, TUNEL, caspase, and actin in paired pre- and post-treatment *tumor* tissues in patients who consented for the optional post-treatment biopsy of the tumors (blood and bone marrow are acceptable if they are known to be involved by lymphoma).
- Explore the correlation of disease response and the PD markers described above.
- Explore the correlation of disease response and gene alternations in tumor tissues.
- Explore the correlation of insulin response and gene alternations in normal buccal fibroblasts.
- Determine the change in body weight and body mass index (BMI) over time.
- Determine the change in computed tomography-based body composition metrics including measures of adipose tissue and skeletal muscle.
- Determine the change in ^{18}F-fluorodeoxyglucose uptake/PET-based adipose tissue and skeletal muscle peak standardized uptake value.

Target Population:

(a) R/R FL, (b) R/R EC with a documented activating mutation in PIK3CA or loss of PTEN.

Inclusion Criteria:

- Be willing and able to provide written informed consent for the trial.
- Be ≥ 18 years of age on day of signing informed consent.
- For lymphoma, patients should have measurable disease based on the Lugano Criteria (Cheson et al., 2014).
- For FL patients must have received at least two lines of prior therapy. There is no upper limit for the number of prior therapies. Tumor tissues of all patients are encouraged to be submitted (optional) prospectively for whole or targeted exome sequencing of key cancer related genes, using the Columbia Combined Cancer Panel (CCCP) or a comparable sequencing platform, such as the MSK-IMPACT 468-gene oncopanel. However, the results of tumor sequencing by themselves are not inclusion criteria for FL. The test should be submitted as per standard of care; however, if the coverage is denied by patients' insurance plans the test will be waivered or if possible paid for by the research protocol.
- For EC the patients must have recurrent/advanced tumor for which surgical or the systemic curative treatments, or standard therapeutic approaches are not available. The following histologic subtypes are eligible: endometrioid, serous, clear cell, undifferentiated/de-differentiated, mucinous, squamous, transitional, not-otherwise specified, and mixed cell-type. EC must have PI3K pathway activation confirmed in mutational profiling using the MSK-IMPACT 468-gene oncopanel or an equivalent platform, as defined below:
  (1) Genomic alteration resulting in loss of PTEN function including a) whole or partial gene deletion, frame shift mutations, or non-sense mutations. Missense mutations in PTEN will not be considered qualifying; OR
  (2) A previously characterized activating mutation in any component of the pathway including: PIK3CA, AKT1, PIK3R1, PIK3R2, and mTOR.
  However, EC must NOT have a known concurrent activating RAS/RAF mutation or loss of function alternation in NF1 of NF2 resulting in MAP kinase pathway activation.
- Fresh and or archived tumor tissues must be available to (a) establish the diagnosis of the respective malignancies as described in Inclusion Criteria, and (b) be investigated for biomarkers. Patients without historical material or fresh tissue biopsy that is adequate for both diagnosis and biomarker studies will not be eligible for the clinical trial. For the lymphoma cohort, bone marrow biopsy can be used for histological confirmation of the diagnosis and for biomarker analyses.

- Left Ventricular Ejection Fraction (LVEF) > 50%.
- A performance status of 0-2 on the ECOG Performance Scale.
- Demonstrate adequate organ function, as described below. All screening labs should be performed within 21 days of initiation of Copanlisib.

Laboratory criteria for inclusion

Laboratory Test	**Criteria**
Glucose	< 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)
Hemoglobin	≥ 8 g/dL [a]
ANC	≥ 1,500/mm^3
Platelets	≥ 75,000/mm^3 [b]
ALT	<2.5 x ULN [c]
AST	<2.5 x ULN [d]
Total bilirubin	within normal limits [e]
GFR (MDRD)	≥ 35 mL/min/1.73 m^2 [f]

ALT = Alanine aminotransferase; ANC = Absolute neutrophil count; AST = Aspartate aminotransferase; GFR = Glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; ULN = Upper limit of normal.

[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 Electronic case report form (eCRF).

[b:] For patients with lymphomatous bone marrow infiltration at study entry (local assessment), platelet count ≥ 50,000/mm3. This value should be used throughout the study irrespective of bone marrow status changes. Platelet transfusion should not be given less than 7 days before the exam collection.

[c:] < 5 x ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

[d:] < 5 x ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

[e:] < 3 x ULN in patients with Gilbert-Meulengracht syndrome, patients with cholestasis due to compressive adenopathies of the hepatic hilum or documented liver involvement by lymphoma.

[f:] If not on target, this evaluation may be repeated once after at least 24 hours either according to the MDRD abbreviated formula or by 24 hour sampling. If the latter result is within acceptable range, it may be used to fulfill the inclusion criteria instead.

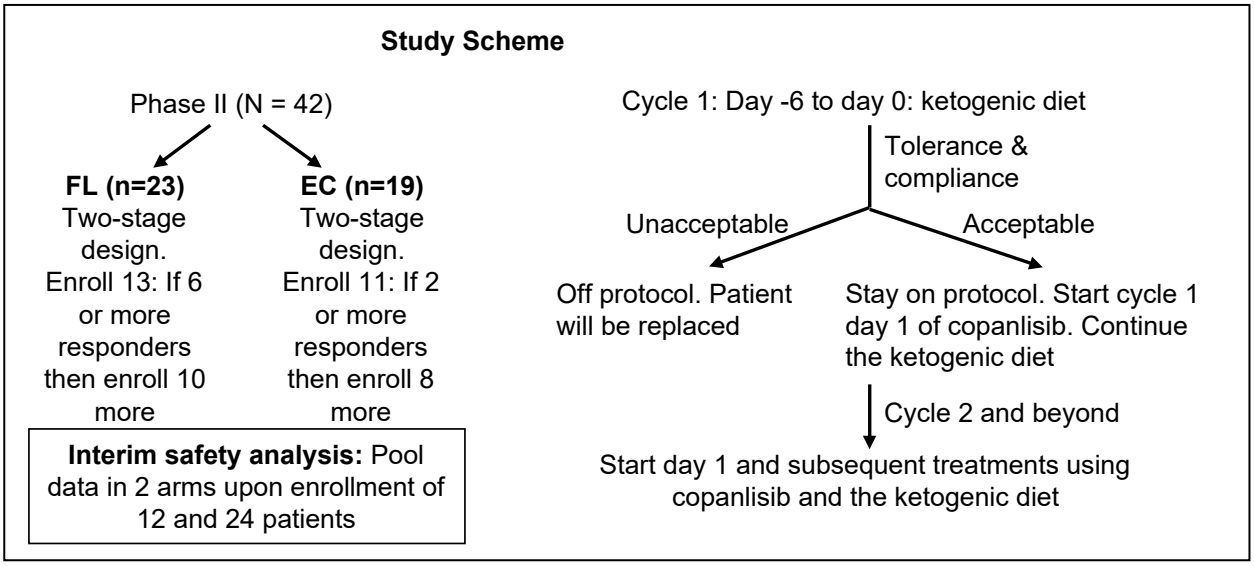
Exclusion Criteria:

- The following treatments are prohibited: (a) Chemotherapy (including PI3K inhibitors and other approved or investigational drugs) and monoclonal antibody within 3 weeks; (b) radiotherapy within 2 weeks prior to entering the study; (c) systemic steroids that have not been stabilized (≥ 5 days) to the equivalent of ≤10 mg/day prednisone prior to the start of the study drugs.
- Patients that have not recovered from adverse events due to chemotherapy agents administered more than 3 weeks earlier.
- Hypersensitivity to copanlisib or any of its excipients.
- Type I diabetes
- Uncontrolled Type II diabetes mellitus (HbA1c> 7.5%).
- Type II diabetes requiring treatment with a sulfonylurea, meglitinide, or insulin.
- Patients that received major surgery and have not recovered adequately from the toxicity

and/or complications from the intervention prior to starting therapy.

- Patients with active, clinically serious infections > CTCAE version 5 Grade 2.
- Patients with known active concurrent malignancy with the following exception: non-melanoma skin cancer, prostatic intraepithelial neoplasia, or carcinoma *in situ* of the cervix, prostate cancer that responds to androgen deprivation therapy and has no progression of disease for at least 12 months. If there is a history of prior malignancy, the patient must be disease-free for ≥ 3 years.
- Uncontrolled hypertension, *i.e.,* blood pressure (BP) of ≥ 150/90; patients who have a history of hypertension controlled by medication must be on a stable dose (for at least one month) and meet all other inclusion criteria.
- Concomitant use of strong CYP3A4 inhibitors.
- Uncontrolled moderate to severe hypertriglyceridemia (TG>300 mg/dL).
- Myocardial infarction within 6 months of cycle 1, day 1. [Subjects with a history of myocardial infarction between 6 and 12 months prior to cycle 1, day 1, who are asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event, may participate].
- Symptomatic coronary artery disease (CAD), *e.g.,* angina Canadian Class II-IV (see Appendix 5). In any patient in whom there is doubt whether the symptoms are truly due to CAD, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present. If the work up is negative the patient may participate in the clinical trial.
- An ECG recorded at screening showing evidence of cardiac ischemia (ST depression of ≥ 2 mm, measured from isoelectric line to the ST segment). In any patient in whom there is doubt whether the ECG changes is accurate and clinically significant, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present. If further work up is negative the patient may participate in the clinical trial.
- Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions and/or ejection fraction < 40% by multigated acquisition (MUGA) scan or < 50% by echocardiogram and/or magnetic resonance imaging (MRI);
- Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks) within 6 months before the start of study medication.
- Patients who are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through at least 30 days after the last dose of trial treatment. History of nephrolithiasis or nephrolithiasis incidentally discovered during CT screening. Known selenium deficiency.
- Body mass index (BMI) less than 20.
- An allergy or intolerance to egg, gluten, tree nuts, peanuts, or milk protein.
- History of serious or uncontrolled gout or hyperuricemia.
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigators' opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.
- Major surgical procedure or significant traumatic injury within 28 days prior to Day 1 or anticipation of the need for major surgery during the course of study treatment.

Study flow chart



The Phase II study will enroll 42 patients in two study groups. The lymphoma study group will enroll 23 patients with FL, and the solid tumor group will enroll 19 patients with EC.

In cycle 1, patients will first start ketogenic diet for 7 days (Day -6 to Day 0). Only patients who demonstrate compliance and tolerance with the ketogenic diet for all 7 days during the run-in phase, as confirmed by pertinent blood and urine tests, will be allowed to continue the study and treatment using copanlisib and the ketogenic diet starting on day 1. In cycle 2 and beyond, patients will start the ketogenic diet and copanlisib on day 1.

Treatment Plan:

- Copanlisib: Copanlisib will be infused intravenously on days d1, 8, 15 of each cycle, over 1 hour, of 28-day cycles.
- Ketogenic diet:
  - Prior to the first treatment patients will start the ketogenic diet for 6 days (Day -5 to Day 0). Patients who demonstrate compliance and tolerance with the ketogenic diet, as confirmed by pertinent blood and urine tests and recorded dietary intake, will be allowed to continue the study and start copanlisib on Day 1. The ketogenic diet will continue daily throughout the treatment days.
  - In cycle 2 and beyond, patients will start the ketogenic diet and copanlisib on day 1. The ketogenic diet will then continue daily throughout the treatment days.
  - All patients will be eligible to receive the ketogenic diet as long as the patients remain on the trial. If patients want to remain on the trial to receive Copanlisib but wish to discontinue the ketogenic diet, they should do so at the following time: (a) when they have achieved a complete response, or (b) when they have completed 4 cycles of treatment. In the rare case when a patient wants to discontinue the ketogenic diet after having completed only 2 or 3 cycles of therapy but having not achieved a CR, the patient will be allowed to remain in the study and receive copanlisib without having to take the ketogenic diet. However, if a patient wishes to stop the ketogenic diet before

cycle 2 is completed, when the response will be first evaluated, the patient will not be allowed to continue this trial but will be replaced.

REGIMEN DESCRIPTION				
Agent	Premedications/Precautions	Dose	Route	Cycle Length
Copanlisib	IV Hydration (Normal Saline 500 cc IV in 30 minutes after copanlisib infusion)	60 mg	IV over 60 minutes	28 days
Ketogenic diet		Three times daily	Oral, three times daily	

Dose Modification:
Dose Modification of copanlisib is described in Section 6.6.

Duration of Treatment:
Patients will be treated until one of the following events: disease progression, unacceptable adverse event(s), withdrawal of consent, general or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

Sample Size and Statistical Consideration:
The study will enroll 42 patients. The two arms will enroll patients in parallel and independently. Safety analysis will be done by pooling patients from the two arms together. Efficacy analysis will be conducted independently within each of the two arms (lymphoma, solid tumor).

Patients who do not complete the planned cycle 2 cycles of treatment, which is required for the first evaluation of response, will be replaced.

(a) The lymphoma arm will enroll 23 patients with FL.

- Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true ORR rate is 41% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are 5 or fewer ORRs **(To be assessed after completing 4 cycles of the treatment)** in these 13 patients, the study will be stopped for futility. Otherwise, 10 additional patients will be accrued for a total of 23. The null hypothesis will be rejected if 14 or more ORRs are observed in 23 patients. This design yields a type I error rate of 5% and power of 80% when the true ORR rate is 67%. Assuming that the CR rate is 0.09 (2 out 23), with 23 subjects we will have 80% power to claim that the true CR is at least 30%.
- The reference range of ORR in FL is 40% (n = 16. Dreyling et al, Ann Oncol. 2017) to

59% (n = 104. Dreyling et al, J Clin Oncol. 2017).
- The reference CR rate is 14% (n = 104. Dreyling et al, J Clin Oncol. 2017).

(b) The solid tumor arm will enroll 19 patients with EC.

- Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true ORR rate is 0.10 will be tested against a one-sided alternative. In the first stage, 11 patients will be accrued. If there are 1 or fewer ORRs **(To be assessed after completing 4 cycles of treatment)** in these 11 patients, the study will be stopped for futility. Otherwise, if >=2/11 responses are observed, then 8 additional patients will be accrued for a total of 19. The null hypothesis will be rejected if 4 or more ORRs are observed in 19 patients. This design yields a type I error rate of 10% and power of 81% when the true ORR rate is 30%.

Safety:
Patients will be monitored carefully for the development of adverse events (AEs). AE will be evaluated according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.

Safety Trigger

There will be ongoing safety monitoring.

Interim safety analysis will be performed upon enrollment of 12 and 24 subjects. Safety analysis will be done by pooling patients from the two arms together.

The safety trigger will be activated if any of the following Safety Trigger Events (STE) happens during the first cycle of treatment:

- During the interim analysis of the first 12 subjects: 3 incidents of STE excluding mortality, or 2 incidents of mortality deemed not likely to be due to progression of the cancer but possibly related to the treatment. The study will be stopped.
- During the interim analysis of the first 24 subjects: 5 incidents of STE excluding mortality, or 3 incidents of mortality deemed not likely to be due to progression of the cancer but possibly related to the treatment. The study will be stopped.

Safety Trigger Events (STE) will defined as the following:

- Any non-hematologic toxicity grade 3-4 that require delay of treatment by more than 7 days despite optimal management.
    - Note that a patient who experiences a STE may be allowed to continue the study, as long as the patient can safely resume therapy within 21 days.
- Any hematologic toxicity grade 3-4 that require delay of treatment by more than 7 days despite optimal management including blood products and growth factors.
    - Note that a patient who experiences a STE may be allowed to continue the study, as long as the patient can safely resume therapy within 21 days.

- Any mortality.

Efficacy Outcome:

Patients will be monitored for clinical and/or radiographic evidence of disease response. Response will be evaluated using clinical parameters, CT or PET/CT scan (PET/CT scan is preferred), and bone marrow or other tissue biopsy (when applicable for lymphoma), according to the Updated Recommendations for Evaluation, Staging, and Response Assessment for Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. For solid tumor the response will be determined in accordance with the revised Response Evaluation Criteria in Solid Tumors

(RECIST) guideline. CT or PET/CT scan will be performed after every two 28-day cycles of. After cycle 4, if the patient has achieved CR, scans will be done every 3 cycles.

Data analysis:

All patients receiving at least one dose of copanlisib will be evaluable for toxicity and all patients completing at least one 28-day cycle of therapy (copanlisib plus ketogenic diet) will be evaluable for response and time-to-endpoint analyses.

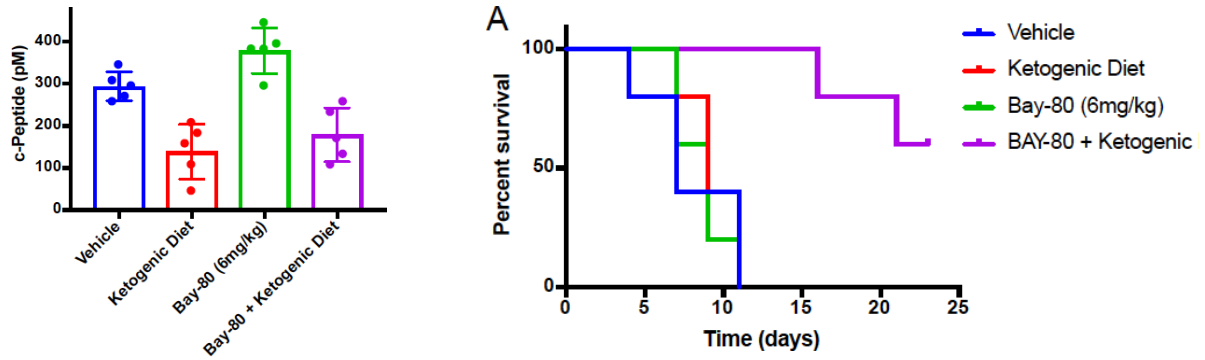
Response will be estimated with exact 95% confidence intervals (CIs). We will estimate overall survival, progression-free survival, and duration of response using the Kaplan-Meier method. Group comparisons, between groups associated with different biomarkers described below, will be made using a two-sided log-rank test, and the estimated hazard ratios and 95% CIs will be calculated using Cox regression. Overall survival will be assessed post hoc in the trial patients.
In the exploratory correlative biomarker analyses, any patients with assessable biological samples (blood, tumor etc) will be included. An association between disease outcome (complete response, partial response, stable disease, progression of disease, duration of response, and progression-free survival) and changes from baseline in biomarker concentrations as a function of treatment over time will be assessed. Because of sample size considerations, we will base group comparisons for these analyses on two-sample t test. We will do correlative studies including all enrolled patients that have adequate biological samples available for analysis. We plan to assess changes over time and estimate odds ratios using mixed-effects logistic regression models or a linear model if the sample sizes for comparison are too small. We will summarize continuous variables as means and SDs, and categorical variables as counts with percentages. We will not do multiple testing adjustments. All the analyses will be done with SAS version 9.4.

<u>Study Rationale</u>

As we recently reported ketogenic diet can suppress hyperinsulinemia associated with PI3K inhibitors, leading to potentiation of the anti-tumor effects of PI3K inhibitors[79]. Copanlisib potently inhibits PI3Kα and PI3Kδ. It has been approved for the treatment of relapsed follicular lymphoma, based on ORR of 59% (84 of 142 patients)[83]. The CR rate in FL was 14%, and the median progression-free survival was 11.2 months. Copanlisib demonstrated encouraging clinical activity in marginal zone lymphoma (ORR 70% including 9% CR). While these results are clinically meaningful, FL and MZL inevitably develop resistance to copanlisib with time, even in those patients who initially respond to the therapy. Novel strategies to improve the efficacy of copanlisib in FL and MZL, by improving CR and PFS, may transform how we manage these incurable malignancies.

Interestingly, copanlisib has also demonstrated clinical activity in aggressive lymphomas in a smaller study of heavily pre-treated patients[84]. Objective responses were achieved in patients with DLBCL (one PR; ORR 6.7%), PTCL (two CRs, one PR; ORR 21.4%), MCL (two uCRs, five PRs; ORR 63.6%), and transformed FL (both PRs; ORR 33.3%). These results suggest that copanlisib warrants further investigation in aggressive lymphomas such as PTCL and DLBCL.
In a Phase I study of both solid tumors and lymphoma, sixteen of 20 patients treated at the MTD had reduced $^{(18)}$FDG-PET uptake; 7 (33%) had a reduction >25%. One patient achieved a complete response (CR; endometrial carcinoma exhibiting both PIK3CA and PTEN mutations and complete PTEN loss) and two had a partial response (PR; both metastatic breast cancer). Among the nine NHL patients, all six with follicular lymphoma (FL) responded (one CR and five PRs) and one patient with diffuse large B-cell lymphoma had a PR by investigator assessment; two patients with FL who achieved CR (per post hoc independent radiologic review) were on treatment >3 years.

The exact mechanism of resistance to copanlisib in various lymphomas and solid tumors remain poorly understood. As described above, we have reported that PI3K inhibitors can induce hyperinsulinemia, which in turn leads to activated survival pathway in cancer cells[79]. Our preliminary results demonstrate that in mice copanlisib stimulated the blood level of insulin, which is effectively mitigated by the ketogenic diet. Importantly, the ketogenic diet markedly improves the survival of KPC mice treated with copanlisib (BAY 80-6946).



(A) Wildtype c57/bl6 mice treated with copanlisib (BAY 80-6946), ketogenic diet, and the combination. c-Peptide levels were accessed from serum samples taken from these animals at the end of the time course, 240 min. (B) Mice with the Kras-Tp53-Pdx-Cre (KPC) tumor allografts were treated as indicated, and the survival of the animals were depicted.

Collectively, the results presented above suggest that copanlisib may have encouraging clinical activity in indolent B-cell NHL such as FL and MZL, aggressive lymphomas such as PTCL and DLBCL, and solid tumors such as endometrial cancer. Furthermore, ketogenic diet may mitigate hyperinsulinemia associated with copanlisib in many patients, leading to improved treatment response to copanlisib and prolonged patient survival.

Fasting requirements and pre-dose glucose levels

Period	**Fasting ≥ 8 h required before first glucose measurement**	**Pre-dose glucose levels (first glucose measurement)**
Day 1 Cycle 1	Yes	≤125 mg/dL (non-diabetic patients) <160 mg/dL (diabetic patients)
Subsequent Infusion after Day 1 Cycle 1	No [a]	<160 mg/dL (fasting) < 200 mg/dL (non-fasting)

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

The investigator will accurately document fasting/non-fasting for each glucose measurement done at the site.

- Fasting refers to no caloric intake for ≥ 8 h.
- Non-fasting status includes any caloric intake such as meals and also juice, snacks, and other caloric intake not consistently called a meal.

From Cycle 1 Day 1 onwards, glucose measurements at the site may be done either by laboratory analysis or in capillary blood using a hand-held glucose meter. If hand-held capillary glucose meters are chosen, the appropriate calibration of glucose meters will be documented. Any capillary or plasma glucose of > 250 mg/dL should be confirmed by repeated laboratory analysis.

Laboratory criteria for dosing of copanlisib

Blood glucose must be performed and assessed on the day of infusion. Glucose lowering medication can be used to optimize pre-infusion glucoses.

Laboratory tests must be performed and assessed prior to each infusion of copanlisib. The results can be done +/- 2 days.

Laboratory criteria for day 1 of each cycle

Laboratory Test	**Criteria**
Glucose	< 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)
Hemoglobin	≥ 8 g/dL [a]
ANC	≥ 1,000/mm^3
Platelets	≥ 75,000/mm^3 [b]
ALT	<2.5 x ULN [c]
AST	<2.5 x ULN [d]
Total bilirubin	within normal limits [e]
GFR (MDRD)	≥ 35 mL/min/1.73 m^2

ALT = Alanine aminotransferase; ANC = Absolute neutrophil count; AST = Aspartate aminotransferase; GFR = Glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; ULN = Upper limit of normal.

[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 Electronic case report form (eCRF).

[b:] For patients with lymphomatous bone marrow infiltration at study entry (local assessment), platelet count ≥ 50,000/mm3. This value should be used throughout the study irrespective of bone marrow status changes. Platelet transfusion should not be given less than 7 days before the exam collection.

[c:] < 5 x ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

[d:] < 5 x ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

[e:] < 3 x ULN in patients with Gilbert-Meulengracht syndrome, patients with cholestasis due to compressive adenopathies of the hepatic hilum or documented liver involvement by lymphoma.

On Days 8 and 15 of each cycle, the dose of copanlisib will be administered only if, on the day of scheduled dosing, the following laboratory test criteria are met (blood tests from the previous day is acceptable):

- ANC ≥ 500/mm^3 (and G-CSF/GM-CSF is mandatory if ANC<1000/mm^3 and should be administered as per label)
- Hemoglobin ≥ 8 g/Dl (Transfusion is allowed)
- Platelet ≥ 75,000/mm^3 (Transfusion is allowed)

Doses of copanlisib may be delayed by up to 2 days. The minimal time between each infusion of copanlisib is 5 days.

A delay of more than 2 days will be considered a missed dose. Missed doses will not be replaced. If a dose is missed by 8-21 days, the patient will start a new cycle at the dose described in Section 6.6 “Dose modification”. If the dose is delayed by more than 21 days, the patient will not be allowed to continue the study. Details were described in Section 5.6 “Withdrawal criteria”.

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