August 12, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #22 to EAY131- Z1F, *Phase II Study of Copanlisib in Patients with Tumors with PIK3CA Mutations (PTEN Loss Allowed).*

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

**IRB Review Requirements:**

**This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study**. Local IRB review and approval is unnecessary.

**Implementation of this addendum must occur on the activation date.** Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

This addendum is in response to Dr. L. Austin Doyle July 29, 2019 Request for Amendment for Copanlisib.

The following revisions to EAY131-Z1F protocol have been made in this addendum:

| | Section | Change |
|---|---|---|
| 1. | Cover Page | Updated version date. |
| 2. | 3.4 | Updated the Copanlisib CAEPR list with version 2.2, June 18, 2019. |

The following revisions to EAY131- Z1F Informed Consent Document have been made in this addendum:

| | Section | Change |
|---|---|---|
| 1. | Page 1 | Updated version date. |
| 2. | "What possible risks can I expect from taking part in this study?" | Updated the Copanlisib risk list with June 18, 2019 version date. |

If you have any questions regarding this addendum, please contact Abuchi Agu at aagu@ecog-acrin.org or 857-504-2900.



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We request review and approval of this addendum to EAY131- Z1F so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Enclosure

CC:

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-Z1F

# Molecular Analysis for Therapy Choice (MATCH)

# MATCH Treatment Subprotocol Z1F: Phase II Study of Copanlisib in Patients with Tumors with PIK3CA Mutations (PTEN Loss Allowed)


COPANLISIB TREATMENT SUBPROTOCOL CHAIR: Senthil Damodaran, MD, PhD

COPANLISIB TREATMENT SUBPROTOCOL CO-CHAIR: Dustin Deming, MD



**Version Date:** August 12, 2019


**NOTE: This subprotocol (EAY131-Z1F) should be used in conjunction with the MATCH Master Protocol (EAY131).**

***SUBPROTOCOL ACTIVATION DATE***

Incorporated in Addendum #13
Addendum #16
Addendum #22

| Agent | IND# | NSC# | Supply |
|---|---|---|---|
| Copanlisib | IND Sponsor: DCTD, NCI | 784727 | NCI Supplied |

# Table of Contents

Rev. Add16

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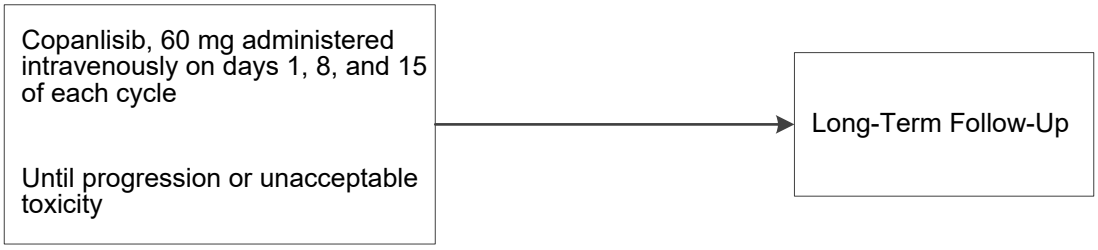
## Schema




Cycle = 28 days
Accrual Goal: 35

# 1. Introduction

## 1.1 Copanlisib

Copanlisib (BAY 80-6946) is a novel, highly selective, PI3K inhibitor with potent activity against both the δ and α isoforms.

## 1.2 Supporting Preliminary Data

### 1.2.1 Rationale

Phosphatidylinositol 3-kinase (PI3K) is involved in tumor cell migration, proliferation, and survival. PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3), which subsequently leads to downstream activation of Akt and associated proteins in the Akt/mammalian target of rapamycin (mTOR) pathway.[1,2] PTEN (phosphatase and tensin or MMAC, mutated in multiple advanced cancers) is a tumor suppressor that negatively regulates the PI3K pathway thorough its phosphatase activity, dephosphorylating PIP3 to PIP2.[3] The loss of PTEN function, observed in multiple tumors, can be caused by various mechanisms including mutations, deletions, transcriptional silencing and epigenetic changes.[4] Activation of the PI3K/AKT/mTOR pathway through *PIK3CA* mutations or PTEN loss is observed in many human cancers.[5,6] Early studies have suggested that *PIK3CA* mutations predict for increased sensitivity to therapies targeting the PI3K/AKT/mTOR signaling pathway.[7,8]

Class I PI3K is a heterodimer with a regulatory and catalytic subunit. The catalytic subunit, p110, has 4 isotypes: alpha, encoded by *PIK3CA*; beta, encoded by *PIK3CB*; gamma, encoded by *PIK3CG*, and delta, encoded by *PIK3CD*. Mutations typically involve the kinase and helical domains of the p110alpha of PI3K.[9] Janku et al analyzed characteristics and outcome of over 1600 patients with diverse advanced tumors and *PIK3CA* mutations. Of 160 patients found to have *PIK3CA* mutations, common mutations included E545K (1633G > A) in 32.5%; E542K (1624G > A) in 20% and H1047R (3140A > G) in 18%.[7] These hotspot mutations in *PIK3CA*, as well as other less common mutations, have been shown to increase the kinase activity of PIK3CA and increase phosphorylation of downstream signaling targets.[10-14] Improved response rates in patients with *PIK3CA* mutations or *PTEN* loss who were treated with Akt inhibitors and PI3K inhibitors compared to patients treated with similar agents but not having *PIK3CA* mutations or PTEN loss, and to patients with *PIK3CA* mutations or PTEN loss treated with agents that do not target the PI3K/AKT/mTOR pathway were observed.[7,8] Patients with *PIK3CA* mutations treated with PI3K/AKT/mTOR inhibitors had a significantly higher partial/complete response (PR/CR) rate (18%) than wild-type *PIK3CA* patients treated with their best phase I therapy (6%), but not prolonged progression-free survival. The rate of stable disease > 6 months/ partial response reached 45% in patients with H1047R *PIK3CA* mutations. *PIK3CA* mutations were more prevalent in patients with *KRAS* mutations than wild-type (WT) *KRAS (*19% versus

9%). Patients with *PIK3CA* mutations and concurrent *KRAS* mutations had a shorter median PFS (1.8 months) compared to patients without *KRAS* mutations (2.9 months). Similarly, response rates were inferior in patients who had concurrent *PIK3CA* and *KRAS* mutations (4%) compared to patients without KRAS mutation (24%). This may be due to complex feedback loops between the MAPK and PI3K pathways such that mTORC1 inhibition leads to ERK1/2 activation via a p70S6K/PI3K/RAS dependent signaling or by mutant KRAS activating $p90^{Rsk1}$ which bypasses mTOR to activate EIF4B and RPS6. Thus, patients with concurrent *KRAS* mutations would be excluded from this study. This trial will assess whether patients with *PIK3CA* mutations show response or have prolonged stable disease with copanlisib.

*Summary of the available preclinical and clinical data from Investigator's brochure is provided below. For additional details, please refer to copanlisib investigator's brochure dated 01 Feb 2016.*

1.2.2 Preclinical Data:

Copanlisib is a pan-class I PI3K inhibitor with dominant PI3Kα (half-maximal inhibitory concentration [IC50]=0.5 nM) and PI3Kδ (IC50=0.7 nM) activity compared to PI3Kβ (IC50=3.7 nM) and PI3Kγ (IC50=6.4 nM) and other protein kinases (inactive at 1 μm, except mammalian target of rapamycin (mTOR) with IC50=45 nM) in biochemical assays. It is also a strong inducer of apoptosis in tumor cells (half-maximal effective concentration [EC50] of 50-400 nM in caspase 9 activation assays in BT474 and BT20 breast cancer cell lines). It has potent and broad in vitro anti-tumor activity (IC50 of 1-760 nM for inhibition of tumor cell proliferation in human breast, ovary, prostate, colon, lung, liver, brain, kidney, melanoma, pancreas, fibrosarcoma, and hematological tumors). It has 100 to 1000-fold cellular selectivity for PI3K vs. mTOR signaling. Of note, several breast cancers, NHL and multiple myeloma cell lines were particularly sensitive to copanlisib (IC50 below 10 nM). Copanlisib was efficacious in tumor cells resistant to herceptin/lapatinib, such as T47D, ZR-75-1, and MCF7. Copanlisib had mean IC50 values of 19 nM against cell lines with *PIK3CA*-activating mutations (N=9), 17 nM against HER2-positive cell lines (N=7), and 17 nM against cell lines with *PIK3CA*-activating mutations and/or HER2 overexpression (N=13), while the activity in *PIK3CA* wild type and HER2-negative cells (N=11) was about 40-fold less potent (average IC50=774 nM). This suggests potent biochemical and cellular activity against PI3Kα, and indicates that *PIK3CA* mutation as a potential biomarker to predict the sensitivity to copanlisib.

In athymic rats, copanlisib showed potent, dose-dependent activity against *PIK3CA* mutation or PTEN-loss xenograft models from various tumor histologies including colon cancer (HCT-116), lung cancer (H460), glioma (U-87 malignant glioma [U87MG]), and breast cancer (KPL-4). The maximum tolerated dose (MTD) in athymic rats was 10 mg/kg (every second day [q2d] ×5, i.v.). Complete tumor stasis was observed at a dose ≥ 3 mg/kg in the four models mentioned above and complete tumor regressions were observed in the KPL-4 (HER2, PIK3CAmut]) breast tumor model. At the 3.0 and

6.0 mg/kg doses, 10 out of 10 nude rats had complete tumor regressions and the animals remained tumor-free (cures) upon termination of the study on Day 73. While HCT-116, H460, and KPL-4 all carry somatic mutation in *PIK3CA*, no tumor regressions were observed in HCT-116 and H460 tumor models. It is possible that the lack of tumor regressions observed in the H460 and HCT-116 models may be due to coexistent *KRAS* mutation leading to activation of alternate MAPK pathway. Synergistic combinational effects with MEK inhibitor refametinib, regorafenib, paclitaxel, and gemcitabine resulted in tumor regression and complete tumor growth inhibition without enhanced general toxicity in patient-derived xenograft models in mice. Synergistic effect of combination of copanlisib with gemcitabine was observed in NSCLC Lu7913 xenograft model, which carries an activating PIK3CA mutation (E545K). Similarly, synergistic effect was observed for the combination of paclitaxel and BAY 84-1236. Combination resulted in a 100% response rate with 4/10 animals exhibiting CR and 6/10 animals having PR, while 60% and 100% animals showed tumor progression in the paclitaxel and BAY 84-1236 monotherapy groups, respectively.

1.2.3 Clinical Data:

As of February 1, 2016, nearly 627 patients with advanced cancers have been treated with copanlisib on multiple studies. Three Phase 1 clinical trials are ongoing and enrolling patients: Study 16790 (copanlisib as monotherapy); Study 16270 (copanlisib with itraconazole / copanlisib with rifampin / cardiovascular safety) and Study 17792 (Japanese indolent NHL patients only). One has completed enrollment but still has one patient under treatment for more than 3 years (FiM [first-in-man] Study 12871), and five are closed (Studies 15205, 12876, 16353, 12874, and 12875). In addition, three Phase 2 clinical trials (Studies 16349, 17119 and 17120) and three Phase 3 trials (Studies 17322, 17067 and 17833) are ongoing. One Phase 2 study has completed enrollment (Study 17119). Study 16349 is an ongoing open-label uncontrolled, parallel group, signal-generating, Phase 2 study to evaluate efficacy and safety of copanlisib as single agent (0.8 mg/kg, maximum 65 mg, i.v. dosing over 1 hour on Days 1, 8, and 15 of each 28-day treatment cycle) in patients with relapsed or refractory, indolent or aggressive NHL. Study 17119 is a single arm, open-label, multicenter Phase II study to evaluate efficacy and safety of copanlisib as single agent in patients with relapsed or refractory DLBCL or DLBCL transformed from FL. Study 17120 is a single-arm, open-label Phase IIa study to evaluate the efficacy and safety of copanlisib monotherapy in patients with relapsed or refractory MCL who progressed after ibrutinib treatment or were unable to tolerate ibrutinib. Study 17322 (CHRONOS-2) is a randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab refractory iNHL who have failed at least two previous lines of therapy. Study 17067 (CHRONOS 3) is a randomized, double-blind, placebo-controlled, two-arm, Phase III study to evaluate efficacy and safety of copanlisib in combination with rituximab, in comparison to placebo in combination with rituximab, in

patients with relapsed iNHL– CHRONOS-3. Study 17833 (CHRONOS 4) is a double-blind, two-arm Phase III study in patients with relapsed, rituximab-sensitive iNHL to evaluate efficacy and safety of copanlisib in combination with standard immunochemotherapy (R-B or R-CHOP) in comparison to standard immunochemotherapy (R-B or R-CHOP) and placebo. Copanlisib has also been studied in healthy volunteers: a mass balance study was conducted in 6 healthy male subjects who received a single i.v. administration of 12 mg [$^{14}$C] copanlisib. Based on pharmacokinetic and clinical data, the recommended dose is 60 mg of copanlisib for all patients given intravenously in a 3 weeks on/1 week off schedule.

1.2.4 Preliminary Pharmacokinetics

Copanlisib demonstrated dose proportional increases in maximum concentration (Cmax) and AUC (area under the plasma concentration-time curve) from time zero to 25 hours (AUC(0-25)) in the dose range 0.1 to 1.2 mg/kg (5 to 93.4 total dose) with a terminal phase half-life (t1/2) of 38.2 hours at a dose of 0.8 mg/kg (n=28). These data indicate that copanlisib is widely distributed in tissues and support a once weekly dosing regimen. No accumulation was observed after once weekly dosing when comparing PK on Cycle 1 Days 1 and 15 and Cycle 3 Day 15. No evidence of time-dependency in the PK of copanlisib was observed. Low extent of plasma protein binding of copanlisib and metabolite M-1 (metabolite of copanlisib) in animals and man with free fractions of 16% (parent compound) and 20% (M-1) in human plasma. The blood/plasma concentration ratio of copanlisib did not change in human blood in the investigated concentration range up to ca. 16000)g/L.

Oxidation and dealkylation at the alkylmorpholine side chain is the major biotransformation pathway in liver microsomes and hepatocytes of various animal species and man; with no major species differences. CYP3A4 is the major metabolizing enzyme in man, while CYP1A1 contributes to a minor extent. Copanlisib was the predominating component in plasma of mouse, rat, dog, and man. M-1 was the only relevant circulating metabolite in plasma of rat and man. In man and rat, balanced elimination of unchanged copanlisib and oxidative biotransformation products via urine and feces were observed. Radioactivity was excreted mainly via the biliary/fecal route in rat, dog, and man after administration of [$^{14}$C] copanlisib. In man, 22% of the administered radioactivity was excreted via urine. [$^{14}$C]. Copanlisib-related radioactivity was secreted into the milk of lactating rats only to a low extent (1.7% of dose). Based on in vitro studies with different cell lines, copanlisib is a substrate of permeability glycoprotein (P-gp) and breast cancer resistance protein (BCRP). There was active uptake of copanlisib into hepatocytes. Organic cation transporters (OCTs), organic anion transporters (OATs) or organic anion transporting polypeptides (OATP) transporters were not involved in hepatic uptake of copanlisib.

There is considered to be low risk for clinical drug-drug interactions through inhibition or induction of major CYP and or uridine diphosphate glucuronosyltransferase (UGT) isoforms or

dihydropyrimidine dehydrogenase by copanlisib. Copanlisib inhibits P-gp (IC50: 7 μM and 7.6 μM for digoxin and dipyridamole, respectively) and BCRP-mediated transport (IC50: 11.5 μM for topotecan); potently inhibits MATE2K (IC50: 0.09 μM for metformin) and inhibits MATE1 (IC50: 10.8μM for metformin). Copanlisib does not inhibit uptake transporters including OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2 or bile salt export pump (BSEP). Drug-drug interactions through inhibition of major CYP and UGT isoforms or P-gp and BCRP by metabolite M-1 are also unlikely. The geometric mean AUC increased by 1.53-fold following 60 mg copanlisib in combination with the strong CYP3A4 inhibitor itraconazole. This increase is considered weak according to FDA drug-drug interaction classification guidance. A population PK model to assess the influence of age, sex, race, body weight, and other size-related covariates (body mass index [BMI], lean body mass [LBM], and BSA) on the pharmacokinetics of copanlisib revealed no apparent correlation between clearance and any of these covariates. Based on these results, there is no indication that a weight-based dose regimen would reduce the variability in exposure of copanlisib.

1.2.5 Preliminary Pharmacodynamics

The PI3K pathway is required for downstream signaling from the insulin receptor. Inhibition of this pathway is expected to lead to impaired cellular uptake of glucose, with a subsequent reactive rise in plasma insulin and glucose levels. Intravenous infusion of copanlisib also causes vasoconstriction, reduced gastrointestinal motility, increased renal volume and electrolyte excretion, and central nervous system (CNS) depressant effects. The CNS depressant effects occur at high drug plasma concentrations and are considered secondary to hyperglycemia. The PD effects on glucose and plasma insulin levels as well as $^{18}$[F] FDG-CT/PET have been investigated in the Study 12871 using copanlisib at different doses. PD effect was defined as having occurred if, within 2 hours after the completion of the infusion, the plasma glucose increased >50 mg/dL from baseline and / or the plasma insulin increased to greater than 2 times the baseline value. All but 1 of the 47 non-diabetic patients treated at 0.4 mg/kg copanlisib experienced a PD effect as well as all 6 diabetic patients treated at 0.4 mg/kg copanlisib. Peak plasma glucose values were seen 5 to 8 hours after the start of the copanlisib infusion. Hyperglycemia was reversible. Dose-related increases in glucose and insulin as well as copanlisib exposure-related increases in plasma glucose were observed. At pharmacodynamically relevant concentrations, copanlisib does not interfere with cardiac repolarization in vitro and in vivo. Other hemodynamic parameters (e.g., heart rate, stroke volume, cardiac output, central venous pressure), ECG intervals (including QT interval) were not affected or only slightly affected. There were no physiologically significant effects on respiration rate, tidal volume, and minute volume.

1.2.6 Safety

When copanlisib was given as a single agent (Study 12871), All 57 patients reported at least 1 treatment-emergent adverse event (TEAE)

by Medical Dictionary for Regulatory Activities Preferred Term (MedDRA PT), regardless of seriousness, severity, and causality, and 49 (86.0%) patients reported at least 1 drug-related TEAE. The most common TEAEs by MedDRA PT, regardless of seriousness, severity, and causality, occurring in ≥ 20% of the 57 patients were: hyperglycemia (64.9%); nausea (54.4%); fatigue (40.4%); diarrhea (33.3%); hypokalemia (31.6%); hypertension (29.8%); vomiting (28.1%); decreased appetite (26.3%); anemia and constipation (24.6% each); dyspnea and dehydration (22.8% each); as well as cough (21.1%). Rash and pruritus were the most frequently reported skin toxicity in 7 (12.3%) These were generally of CTCAE v3.0 Grade 1 or Grade 2 in severity, only 4 (7.0%) patients experienced Grade 3 skin/subcutaneous disorders. Rash was generally manageable with topical steroids but systemic steroids were sometimes needed.

The most common drug-related TEAEs by MedDRA PT, regardless of seriousness and severity, occurring in ≥20% of the 57 patients (all cohorts) were: hyperglycaemia (63.2%), nausea (38.6%), and hypertension (21.1%). The most common drug-related TEAEs by MedDRA PT with a severity of CTCAE v3.0 Grade ≥ 3 occurring in ≥ 5% of the 57 patients (all cohorts) were: hyperglycemia (39.0%) and hypertension (17.1%). Increased blood pressure (BP) is frequently observed within the first 3 hours after start of infusion. Five (8.8%) patients experienced any TEAE leading to dose reduction. These TEAEs by MedDRA PT were: exfoliative rash, hyperglycemia, dyspnea, mucosal inflammation (one patient each), anemia and thrombocytopenia in 1 same patient. Ten patients experienced any TEAE leading to permanent discontinuation of study drug. The 10 serious TEAEs leading to permanent discontinuation of study drug in the 9 patients were: aspiration pneumonia, ascites/oedema, enterococcal sepsis, LVEF dysfunction/cardiac tamponade, intracranial hemorrhage, large intestinal obstruction, portal vein thrombosis, staphylococcal bacteraemia and pleural effusion. Except the LVEF (DLT in Cohort 1.2 mg/kg), none of these TEAEs was assessed as drug-related by the investigators. Hyperglycemia due to copanlisib is reversible. Copanlisib was not discontinued in any patient due to hyperglycemia. The other common laboratory abnormalities (occurred in most patients) included: hemoglobin decreased in 49 of 57 patients (89.1%); hypoalbuminaemia in 43 of 56 patients 76.8%); hypocalcaemia in 38 of 55 patients (69.1%); leukocytes decreased in 37 of 55 patients (67.3%); AP increased in 37 of 56 patients (66.1%); lymphopenia was documented in 17 of 28 patients (60.7%); AST increased in 33 of 56 patients (58.9%); and hypercholesterolaemia was seen in 2 of 4 patients (50.0%). AST increase, considered a class effect, was observed mainly with a severity of CTCAE v3.0 Grade 1 (42.9%). In Study 16349 Part A, the most common TEAEs experienced by > 20% of the study population were hyperglycemia (59.3%), hypertension (56.8%), diarrhea (40.7%), fatigue (35.8%), nausea (32.1%), neutropenia (28.4%) and anemia (27.2%). Pneumonitis occurred in 3 patients with FL; no pneumonitis was reported in solid tumor patients. Copanlisib is expected to adversely affect male and female reproduction, based on findings

from the repeat-dose toxicity studies. Due to the mechanism of action of copanlisib as a PI3K inhibitor, adverse effects on development and reproduction are expected. Copanlisib is not mutagenic in vitro or in vivo. There is no evidence for a phototoxic potential of copanlisib. 60 mg of copanlisib (given in a 3 weeks on/1 week off schedule) is expected to have a comparable safety profile to the observed safety profile at the MTD of 0.8 mg/kg.

1.2.7 Efficacy

In the Phase 1 monotherapy Study 12871, out of the 48 patients with solid tumors, CR as best overall response was achieved in 1 patient (2.1%) with endometrial cancer, 2 patients (4%) had PR, 15 (31%) achieved SD, and 15 (31%) had disease progression by investigator assessment, according to RECIST version 1.1. Seven patients (15%) had disease progression by clinical judgment and 8 patients (17%) were not assessed. Clinical benefit (CR, PR, or SD) was observed in 18 patients (38%) overall, by investigator assessment. Patient with CR (after 10 cycles of copanlisib) was a 75-year-old woman with poorly differentiated uterine adenocarcinoma (Stage IV at study entry). The archival tumor tissue of this patient exhibited mutations in both *PIK3CA* and *PTEN* by next-generation sequencing (NGS) as well as complete PTEN loss by IHC. Among the 9 NHL patients, all 6 with FL responded (one CR and 5 PRs) and one patient with diffuse large B-cell lymphoma had a PR; 2 patients with FL achieved CR (per subsequent post hoc independent radiologic review), and 2 FL patients were on treatment > 3 years. In the Phase II Study 16349 Part A, ORR analyzed by histological subtype showed that in the indolent NHL group, the ORR was 47.37% in indolent B-cell lymphoma (N=19), 40.00% in FL (N=15), 38.46% in CLL (N=13), 66.67% in MZL (N=3), and 100% in SLL (N=1). In the aggressive NHL group, the best ORR (>30%) were observed in MCL (63.64%, N=11) and in transformed indolent lymphoma (33.33%, N=6).

## 2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

**In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.**

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

**NOTE:** Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

**NOTE:** Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

**NOTE:** All patients must have signed the relevant treatment consent form

### 2.1 Eligibility Criteria

_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

_____ 2.1.2 Patients must have PIK3CA mutation as determined via the MATCH Master Protocol and described in Appendix I. See Appendix I for information on the eligible PIK3CA alterations and corresponding Levels of Evidence.

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date of ECG: _____

_____ 2.1.4 Patients must not have known hypersensitivity to copanlisib or compounds of similar chemical or biologic composition.

_____ 2.1.5 Patients must not have had prior therapy with copanlisib or other PI3K inhibitors, AKT inhibitors or mTOR inhibitors.

_____ 2.1.6 Patients must not have activating KRAS mutations. See Appendix I for a list excluded *KRAS* mutations.

_____ 2.1.7 Patients must not have HER2 positive (3+ by IHC or FISH ratio ≥ 2) breast cancer.

_____ 2.1.8 Patients must not have indolent NHL (follicular lymphoma, SLL/CLL, LPL, marginal zone lymphoma) or DLBCL (diffuse large B cell lymphoma).

_____ 2.1.9 Patients must not be on strong inhibitors or inducers of CYP3A4 within two weeks prior to start of study treatment and for the duration of study treatment.

_____ 2.1.10 Patients should stop using herbal medications at least 7 days prior to the first dose of copanlisib. Herbal medications include, but are not limited to: St. John's Wort, Kava, ephedra, gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng.

Rev. Add16 _____ 2.1.11 Patients with Type I or II diabetes mellitus must have HbA1c ≤ 8.5% within 28 days from registration.

_____ 2.1.12 Patients must not be on anti-arrhythmic therapy other than digoxin or beta-blockers.

Rev. Add16 _____ 2.1.13 Patients must have adequate marrow function as defined below:

- ANC ≥ $1.5x10^9$ /L
- Platelets ≥ $100x10^9$ /L
- Hb > 9 g/dl

Rev. Add16 _____ 2.1.14 Patients must have adequate organ function as defined below:

- Total serum bilirubin < 2.0 mg/dL,
- ALT and AST < 2.5x ULN (< 5x ULN in patients with liver metastases),
- Serum creatinine < 1.5x ULN

Rev. Add16 _____ 2.1.15 Patients with non-healing wound, ulcer, or bone fracture are not eligible.

_____ 2.1.16 Patients with history of or current interstitial pneumonitis are not eligible.

**NOTE:** For solid tumors, CMV PCR can be obtained at the discretion of treating physician or local institutional guidelines.

_____ 2.1.17 Men and women of child-bearing potential must agree to use contraception while receiving study treatment and for 1 month after the last dose of copanlisib.

Physician Signature Date

**OPTIONAL:** This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

## 3. Copanlisib Treatment Plan

### 3.1 Dosage and Administration Schedule

Copanlisib is given intravenously at a dose of 60 mg over 1 hour on day 1, 8, and 15 in a 3 week on/1 week off schedule. Each cycle is 28 days and cycles are repeated until progression. Please see Section 3.5 for dose modifications.

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

Rev. Add16

**Blood pressure measurement on treatment days**

Blood pressure will be measured prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results <150/90 mmHg with at least a 15 min interval between the measurements to be able to start the infusion of the study medication (pre-dose). The investigator can consider a medical intervention to maintain blood pressure in values appropriate for infusion. The investigator must delay the infusion until blood pressure values are below 150/90.

On copanlisib infusion days, blood pressure will be measured at pre dose, 30 min after the start of infusion, right after the end of infusion; and 1 h and 2 h after the end of copanlisib infusion.

**NOTE:** Time window of ± 10 min is allowed for all post dose blood pressure measurements.

Rev. Add16

**Recommendations on meal timing on copanlisib infusion days**

Because of an inhibitory effect on PI3Kα-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporary increase in blood glucose. Consuming meals in close proximity to copanlisib infusion may exacerbate a glucose level increase**.**

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

All glucose measurements done at the site, oral glucose lowering medication and/or insulin administration, if applicable, pre-dose fasting/non-fasting status and meal intake timing on infusion days should be documented.

Rev. Add16

**Pre-dose glucose levels**

| Period | Pre-dose glucose levels |
|---|---|
| **Day 1 of cycle 1** | < 160 mg/dL (fasting)<br>< 200 mg/dL (non-fasting) |
| **Day 1 of subsequent cycles** | < 160 mg/dL (fasting)<br>< 200 mg/dL (non-fasting) |
| **Days 8 and 15 of each cycle** | < 160 mg/dL (fasting)<br>< 200 mg/dL (non-fasting) |

The study drug will be administered only if pre-dose glucose level is < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting).

Glucose monitoring is required before and after each copanlisib infusion. The glucose testing is scheduled as follows:

- On Cycle 1 Day 1: Glucose test (finger stick or serum glucose) is performed before starting copanlisib IV infusion at time 0 hour. Additional measurements to be performed at the clinic as clinically indicated at the investigator's discretion.
- On Cycle 1 Days 8 and 15 and all treatment days in subsequent cycles: Glucose test (finger stick or serum glucose) is performed before starting copanlisib IV infusion at time 0 hour. Additional measurements to be performed at the clinic as clinically indicated at the investigator's discretion).
- Review of the blood glucose measurements/meal timing/insulin administration/oral glucose lowering medication, if applicable.

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

**Monitoring of diabetic patients**

- If the patient already monitors his/her blood glucose as part of routine antidiabetic care, the routine measurements should not be replaced by the study specific measurements.

## 3.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of copanlisib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The known potential targets for drug interaction are CYP3A4 inducers or inhibitors, as well as drugs modulating glucuronidation, P-gp, BCRP, and MATE2K function. Appendix II (Patient Drug Information Handout and Wallet Card) should be provided to patients.

Substrates of P-gp and/or BCRP with narrow therapeutic index should be used with caution and patients monitored for any sign of toxicity. Furthermore, sensitive substrates of the renal drug transporter MATE2K (*e.g.* metformin) need to be used with caution. Metformin should be interrupted for 48 hours after receiving iodinated contrast media.

Patients taking medications with narrow therapeutic index should be proactively monitored if these medications cannot be avoided. These medications may include quinidine, cyclosporine, and digoxin.

Patients should stop using herbal medications at least 7 days prior to the first dose of copanlisib. Herbal medications include, but are not limited to: St. John's Wort, Kava, ephedra, gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng.

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

## 3.3 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 sub-protocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

### 3.3.1 Additional instructions, requirements and exceptions for protocol EAY131 – Subprotocol Z1F

**Additional Instructions**

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

**EAY131 – Subprotocol Z1F specific expedited reporting requirements:**

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on copanlisib, or within 28 days of the subject's last dose of copanlisib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

**EAY131 – Subprotocol Z1F specific expedited reporting exceptions:**

For Subprotocol Z1F, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

3.3.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

**NOTE:** The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

**NOTE:** If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be

submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

**NOTE:** Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. Add22

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 702 patients.* Below is the CAEPR for Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride).

**NOTE:** If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

**Version 2.2, June 18, 2019[1]**

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

| Adverse Events with Possible Relationship to Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CTCAE 5.0 Term) [n= 702] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | | Erythroderma | |
| | | Pruritus | |
| | Rash maculo-papular | | ***Rash maculo-papular (Gr 2)*** |
| VASCULAR DISORDERS | | | |
| Hypertension | | | ***Hypertension (Gr 2)*** |

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

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

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

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

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Eosinophilia

**CARDIAC DISORDERS** - Atrial fibrillation; Cardiac arrest; Left ventricular systolic dysfunction; Myocardial infarction; Sinus tachycardia

**GASTROINTESTINAL DISORDERS** - Abdominal pain; Colitis; Constipation; Dry mouth; Dyspepsia; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Oral dysesthesia; Oral pain; Upper gastrointestinal hemorrhage

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Death NOS; Fever; General disorders and administration site conditions - Other (failure to thrive); Non-cardiac chest pain

**IMMUNE SYSTEM DISORDERS** - Allergic reaction; Autoimmune disorder

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Fracture; Infusion related reaction; Injury, poisoning and procedural complications - Other (drug eruption)

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; Investigations - Other (electrocardiogram U wave abnormal); Lipase increased; Lymphocyte count decreased; Serum amylase increased

**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (blood insulin increased)

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthralgia; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (psoriatic arthropathy); Myalgia

**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor hemorrhage

**NERVOUS SYSTEM DISORDERS** - Amnesia; Dizziness; Dysesthesia; Dysgeusia; Headache; Paresthesia; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome

**PSYCHIATRIC DISORDERS** - Confusion

**RENAL AND URINARY DISORDERS** - Acute kidney injury; Renal and urinary disorders - Other (renal insufficiency)

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Cough; Dyspnea[3]; Hypoxia; Pleural effusion; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pulmonary congestion)

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Purpura; Rash acneiform; Stevens-Johnson syndrome

**VASCULAR DISORDERS** - Hypotension; Thromboembolic event; Vascular disorders - Other (circulatory collapse)

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

Rev. Add16

## 3.5 Dose Modifications

**All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.**

**All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).**

The side effects observed with copanlisib (BAY 80-6946) are consistent with those observed with other PI3K inhibitors.

Copanlisib will be administered at fixed dose (60 mg) intravenously on Days 1, 8, and 15 on a 28-Day cycle. Copanlisib dose reduction instructions provided in **Table 1** serve as guidelines to allow ongoing treatment for patients without signs or symptoms of progression while monitoring patient safety. If there is need to interrupt dosing for grade 3/4 toxicity, then there will be a dose reduction as per the table below, once toxicity improves to grade 1 or baseline. Selected toxicities / adverse events of interest for copanlisib include hyperglycemia, rash, hypertension, diarrhea.

**Table 1 Overall Dose Modification Guideline for Copanlisib (BAY 80-6946)-Related Adverse Events**

| | Copanlisib |
|---|---|
| Starting dose | 60 mg |
| First reduction | 45 mg |
| Second reduction | 30 mg |

Dose may be suspended for up to 4 weeks due to toxicity. Patients requiring treatment to be held for >4 weeks will be taken off treatment. If treatment held for laboratory abnormality, recheck labs in one week. No dose reduction is allowed for patients treated at a dose 30 mg of copanlisib – if there is an indication for further dose reduction, the patient must permanently discontinue copanlisib. Dose re-escalation is not allowed after a dose reduction.

Rev. Add16

**Dose Modification rules for transient post-infusion hyperglycemia**

Patients who develop post-infusion glucose increases of grade 2 after study drug administration may continue treatment. However, the next infusion must be delayed until the patient's pre-infusion glucose levels return to < 160 mg/dL (fasting) or < 200mg/dL (non-fasting). Guidelines for the management of transient glucose increases are given in Appendix III. Continuing occurrence of post-infusion blood glucose increases of grade ≥ 3, despite optimal glucose lowering therapy after 2 infusions of copanlisib, will require dose reduction by one dose level.

- Further dose reduction **(where appropriate per study design/population)** is allowed as long as discontinuation criteria was not met.
- Dose re-escalation is allowed when a patient has achieved controlled glucose levels per investigator's judgment.

- Occurrence of post-infusion non-life threatening hyperglycemia requiring interventions at the protocol defined lowest dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) requires permanent discontinuation of the study drug.
- Occurrence of post infusion life-threatening copanlisib related hyperglycemia requires permanent discontinuation of the study drug.

### Management of Hyperglycemia

Metformin is the first antihyperglycemic medication of choice because of the lower risk of hypoglycemia with this agent. Because metformin in some patients may also cause diarrhea and can be poorly tolerated, other antihyperglycemic medications such as sulfonylureas (e.g. glimepiride, glipizide) can be used. Extra caution should be used with other drugs such as sulfonylureas because of the increased risk for hypoglycemia with these agents. Consultation with an endocrinologist can be helpful in managing hyperglycemia.

Insulin should only be used for patients with persistent, symptomatic hyperglycemia. It should not be used to lower glucose level on the day of infusion due to the risk of hypoglycemia. On treatment days, it is best to hydrate the patient and not give insulin to reduce glucose levels to meet study treatment criteria.

Management guidelines for fasting patients with hyperglycemia are listed below in Table 2.

**Table 2: Management of Hyperglycemia**

| Grade | Intervention | Dose Adjustment |
|---|---|---|
| 1 | Initiation of an oral anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring should be considered. | No change. |
| 2 | Initiation or increased dose of an oral anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring should be considered. | Dosing with copanlisib may either be held or continued per Investigator evaluation. |
| 3, asymptomatic | Patient should be managed as per standard care, including implementation of additional glucose monitoring and initiation and/or increase of anti-hyperglycemic therapy (e.g., metformin). | Consideration should be given to suspend copanlisib dosing until the hyperglycemia resolves to Grade ≤ 2. Dosing with copanlisib may resume at the same dose level or at one dose level lower as outlined in Table 1 and after discussion with the Study Principal Investigator. |
| 3, symptomatic (e.g., blurred vision, frequent urination, excessive thirst) or grade 4 | Patient should be managed as per standard care, including implementation of additional glucose monitoring and initiation and/or increase of anti-hyperglycemic therapy | Copanlisib dosing should be suspended until the hyperglycemia resolves to Grade ≤ 2. The patient will be discontinued from the study if such therapy fails to control their hyperglycemia. Dosing with copanlisib may otherwise resume at one dose level lower as outlined in Table 1. |

*Based on fasting glucose level

### Management of Rash

Treatment related rash has been reported with copanlisib. While most were CTCAE v3.0 Grade 1 or Grade 2 in severity, few patients experienced Grade 3 rash. Rash is generally macular or maculo-papular with or without pruritus, with some having developed desquamation. Patients with severe rash should be monitored for associated signs and symptoms, such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, hold all study treatment until Grade $\leq 1$ (see Table 3 below), and patients should be treated with supportive therapy per standard of care. Use of topical antihistamine, as well as topical or systemic corticosteroids, may be considered. There is no evidence for a phototoxic potential of copanlisib.

**Table 3: Dose Delay and Modification Guidelines for Rash**

| Grade | Intervention | Dose Adjustment |
|---|---|---|
| Grade 1 | Consider prescribing topical corticosteroids [a] | Continue dosing at current dose and monitor for change in severity. |
| Grade 2 | Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]). | Consider holding copanlisib or reducing to the next lower dose if rash is troublesome. |
| Grade 3 or 4 | Consider treatment with supportive therapy (e.g., topical or oral corticosteroids [a, b]).<br>Consider dermatological consultation.<br>Consider obtaining photographs of rash if permitted by local regulations. | Hold all study treatment until Grade $\leq 1$.<br>For Grade 3, restart copanlisib at the next lower dose upon discussion with Overall Principal Investigator, or permanently discontinue treatment.<br>For Grade 4, permanently discontinue treatment |

a Suggested topical steroids include, hydrocortisone 2.5% to face twice daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body bid.

b Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg $\times$ 2 days, 40 mg $\times$ 2 days, 20 mg $\times$ 2 days, etc.).

### Management of Hypertension

Patients receiving copanlisib who have experienced hypertension and blood pressure should be monitored at each visit. In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 2 minutes later, with the two readings averaged to obtain a final BP measurement.

For patients who develop HTN or worsening HTN during study treatment, antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study treatment at the discretion of the investigator. If hypertension is persistent despite adequate anti-HTN therapy including titration of anti-HTN medication or introduction of additional anti-HTN medications, dose interruption, reduction or discontinuation is recommended. If Grade 4 HTN develops, permanently discontinue treatment. Patients with prior history of hypertension (on anti-hypertensive agents) should monitor/record their BP at home while on copanlisib.

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

The management of acute blood pressure (BP) increases following copanlisib will need to be individualized for each patient, but experience from a Bayer-sponsored phase 1 study with copanlisib has suggested the benefit of dihydropyridine calcium channel blockers (*i.e.,* amlodipine, felodipine). 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 anti-hypertensive medication is readily available in case of need.

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

Rev. Add16

**Blood pressure measurement on treatment days**

Blood pressure will be measured prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results < 150/90 mmHg with at least a 15 min interval between the measurements to be able to start the infusion of the study medication (pre-dose). The investigator can consider a medical intervention to maintain blood pressure in values appropriate for infusion. The investigator must delay the infusion until blood pressure values are below 150/90.

On copanlisib infusion days, blood pressure will be measured at pre dose, 30 min after the start of infusion, right after the end of infusion; and 1 h and 2 h after the end of copanlisib infusion.

**NOTE:** Time window of ± 10 min is allowed for all post dose blood pressure measurements.

| Event | Management Guideline | Dose Modification |
|---|---|---|
| Definitions used in the table:<br>- Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits.<br>- Well-controlled hypertension: Blood pressure of SBP ≤150 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits.<br>- Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.<br>- Asymptomatic hypertension: SBP >150 mmHg and/or DBP >90 mmHg in the absence of the above symptoms. | | |
| **(Scenario A)**<br>• Asymptomatic and persistent SBP of ≥150 and <160 mmHg, or DBP ≥90 and <100 mmHg,<br>OR<br>• Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg). | • Adjust current or initiate new antihypertensive medication(s).<br>• Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B). | • Continue copanlisib at the current dose. |
| **(Scenario B)**<br>• Asymptomatic SBP ≥ 160 mmHg, or DBP ≥ 100mmHg,<br>OR<br>• Failure to achieve well-controlled BP within 2 weeks in Scenario A. | • Adjust current or initiate new antihypertensive medication(s).<br>• Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. | • Interrupt copanlisib.<br>• Once BP is well-controlled, restart copanlisib at a reduced dose. |
| **(Scenario C)**<br>• Symptomatic hypertension<br>OR<br>• Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment | • Adjust current or initiate new antihypertensive medication(s).<br>• Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.<br>• Referral to a specialist for further evaluation and follow-up is recommended.<br>• Continue follow-up per protocol. | • Discontinue copanlisib. |
| **(Scenario D)**<br>• Refractory hypertension unresponsive to above interventions or hypertensive crisis. | • Continue follow-up per protocol. | • Discontinue copanlisib. |

### Non-infectious pneumonitis

The investigator is requested to differentiate between non-infectious pneumonitis, and infectious pneumonitis (viral, bacterial, or fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion; and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".

In the event of suspected non-infectious pneumonitis, modify copanlisib treatment as per table below.

**Dose adjustment for non-infectious pneumonitis**

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

NA = Not applicable; NIP = Non-infectious pneumonitis; CTCAE = Common Terminology Criteria for Adverse Events.

a: Not applicable for 45 mg dose level. No re-escalation is allowed after the dose reduction.

Rev. Add16 The lowest dose level for patients with non-infectious pneumonitis is 45 mg; if a patient is already on the 45 mg dose level and cannot tolerate treatment study treatment will be discontinued permanently.

Rev. Add16 **Dose modifications for Hematological Toxicities**

| Day | ANC | | Platelets | Dose modifications |
|---|---|---|---|---|
| Day 1 | ≥ 500/uL | AND | ≥ 75,000/uL | Treat at current dose level |
| | < 500/uL | OR | < 75,000/uL | Delay until count recovery |

Use of WBC growth factors is allowed as per institutional guidelines for treatment or prevention of complication. Use of WBC growth factors to maintain dose intensity is not allowed.

**Dose Modifications for General Non-hematologic Toxicities**

This section does not refer to those non-hematologic toxicities for which dose modifications are listed above.

| Grade | Action and Dose Modification |
|---|---|
| Grade 1 or transient Grade 2 | No intervention |
| Grade 2 lasting ≥ 7 days with optimal/best supportive care | Hold Copanlisib<br>Resume at 60 mg after recovery to ≤ grade 1<br>Recurrence at 60 mg: Hold Copanlisib<br>Resume at 45 mg after recovery to ≤ grade 1<br>Recurrence at 45 mg: Hold Copanlisib<br>Resume at 30 mg after recovery to ≤ grade 1<br>Recurrence at 30 mg: Discontinue Copanlisib |
| Grade 3 | Hold Copanlisib<br>Resume at 45 mg after recovery to ≤ grade 1<br>Recurrence at 45 mg: Hold Copanlisib<br>Resume at 30 mg after recovery to ≤ grade 1<br>Recurrence at 30 mg: Discontinue Copanlisib |
| Grade 4 | Discontinue treatment |

*Copanlisib will be discontinued if treatment delay is > 4 weeks*

3.6 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study. Diarrhea, nausea and vomiting have all been reported with copanlisib. Supportive measures with anti-diarrheals and anti-emetics are recommended per investigator discretion or local institutional guidelines for emergence of treatment related symptoms.

3.7 Duration of Agent-specific treatment

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.8 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

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# 4. Study Parameters

## 4.1 Therapeutic Parameters for Copanlisib Treatment

**NOTE:** In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving Copanlisib treatment.

**NOTE:** All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

| Test/Assessment | Prior to Registration to Treatment | Treatment | | End of Treatment | Follow Up[F] |
|---|---|---|---|---|---|
| | | Every Cycle, prior to treatment | Every 2 Cycles | | |
| H&P, Weight, Vital signs[A] | X | X[I] | | | X |
| Performance status | X | X[I] | | | X |
| CBC w/diff, plts[B] | X | X[I] | | | X |
| Serum chemistry[B] | X | X[I] | | | X |
| Glucose monitoring[K] | | X | | | |
| Hemoglobin A1c[L] | X | | | | |
| Radiologic evaluation[D] | X | | X[D] | | X[F] |
| β-HCG[C] | X | | | | |
| Toxicity Assessment[G] | | X | | X | X[F] |
| ECG[J] | X | X[H] | | | |
| Tumor biopsy and blood sample for MATCH Master Protocol[E] | | | X | X | |

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle). Blood pressure will be measured prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results < 150/90 mmHg. On copanlisib infusion days, blood pressure will be measured at pre dose, 30 min after the start of infusion, right after the end of infusion; and 1 h and 2 h after the end of copanlisib infusion. Time window of ± 10 min is allowed for all post dose blood pressure measurements. Refer to Section 3.1.

B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, fasting glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease. Please refer to the table in Section 3.1 regarding “Pre-dose glucose levels.”

C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

H. As clinically indicated.

I. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this time point: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

J. Within 8 weeks of treatment assignment.

K. On Cycle 1 Day 1, glucose test (finger stick or serum glucose) is performed before starting copanlisib IV infusion at time 0 hour. On Cycle 1, Days 8 and 15 and all treatment days in subsequent cycles, glucose test is performed before starting copanlisib IV infusion at time 0 hour. Additional measurements to be performed at the clinic as clinically indicated at the investigator's discretion. Refer to Section 3.1.

L. Hemoglobin A1c (HbA1c) is to be tested at screening if patient has Type I or II diabetes mellitus. Refer to Section 2.1.11.

## 5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

### Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

**NCI Supplied Agent(s) – General Information**

**Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.**

**Drug Returns:** All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

**Drug Accountability:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

**Investigator Brochure Availability:** The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

## 5.1 Copanlisib (NSC #784727)

### 5.1.1 Other Names

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

### 5.1.2 Classification

Pan class I PI3K inhibitor

### 5.1.3 Mode of Action

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

### 5.1.4 Storage and Stability

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

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

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

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

### 5.1.5 Dose Specifics

60 mg of intravenous copanlisib (1 hour infusion) would be administered on Days 1, 8, 15 every 28 days (3 weeks on/1 week off)

### 5.1.6 How Supplied

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

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5.1.7 Preparation

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

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5.1.8 Route of Administration

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

5.1.9 Incompatibilities

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

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

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

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

5.1.10 Side Effects

See Section 3.4 for side effects

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5.1.11 Nursing/Patient Implications

Females of reproductive potential and males must use effective contraception while receiving study treatment and for 1 month after the last dose of copanlisib. Females should not breastfeed during treatment with copanlisib and for at least 1 month after the last dose of copanlisib.

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

Section 3.5 and Appendices III and IV for treatment and monitoring guidelines.

## 6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

## 7. References

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**Molecular Analysis for Therapy Choice (MATCH)**
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## Appendix I

## Actionable Mutations for Sub-Protocol EAY131-Z1F

*Inclusion Variants*

Other novel PIK3CA activating mutations not listed in the table below but identified by one of the designated outside laboratories as described in the MATCH Master Protocol will also be considered actionable mutations (aMOIs) at Level of Evidence Code 3. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

| Gene Name | Variant ID | Variant Type | Level of Evidence Code | Variant Description |
|---|---|---|---|---|
| PIK3CA | COSM746 | SNV | 2 | p.R88Q |
| PIK3CA | COSM754 | SNV | 2 | p.N345K |
| PIK3CA | COSM757 | SNV | 3 | p.C420R |
| PIK3CA | COSM759 | SNV | 3 | p.P539R |
| PIK3CA | COSM760 | SNV | 3 | p.E542K |
| PIK3CA | COSM763 | SNV | 3 | p.E545K |
| PIK3CA | COSM764 | SNV | 3 | p.E545G |
| PIK3CA | COSM765 | SNV | 2 | p.E545D |
| PIK3CA | COSM767 | SNV | 3 | p.Q546P |
| PIK3CA | COSM775 | SNV | 2 | p.H1047R |
| PIK3CA | COSM776 | SNV | 3 | p.H1047L |
| PIK3CA | COSM12458 | SNV | 3 | p.E545A |
| PIK3CA | COSM766 | SNV | 3 | p.Q546K |
| PIK3CA | COSM12590 | SNV | 3 | p.T1025S |
| PIK3CA | COSM12591 | SNV | 3 | p.M1043V |
| PIK3CA | COSM29313 | SNV | 3 | p.M1043I |
| PIK3CA | COSM94984 | SNV | 3 | p.M1043I |
| PIK3CA | COSM773 | SNV | 3 | p.M1043I |
| PIK3CA | COSM774 | SNV | 3 | p.H1047Y |
| PIK3CA | COSM27493 | SNV | 3 | p.R93W |
| PIK3CA | COSM748 | SNV | 3 | p.G106V |
| PIK3CA | COSM13570 | SNV | 3 | p.K111E |
| PIK3CA | COSM751 | SNV | 3 | p.G118D |
| PIK3CA | COSM94978 | SNV | 3 | p.N345I |
| PIK3CA | COSM762 | SNV | 3 | p.E542V |
| PIK3CA | COSM6147 | SNV | 3 | p.Q546E |

| Gene Name | Variant ID | Variant Type | Level of Evidence Code | Variant Description |
|---|---|---|---|---|
| PIK3CA | COSM12459 | SNV | 3 | p.Q546R |
| PIK3CA | COSM27504 | SNV | 3 | p.N1044K |
| PIK3CA | COSM12592 | SNV | 3 | p.N1044K |
| PIK3CA | COSM12597 | SNV | 3 | p.G1049R |
| PIK3CA | COSM12584 | SNV | 3 | p.E453K |
| PIK3CA | COSM27133 | SNV | 3 | p.E545Q |
| PIK3CA | COSM27505 | SNV | 3 | p.K111N |
| PIK3CA | COSM12580 | SNV | 3 | p.K111N |

*Exclusion Variants*

| Gene Name | Variant ID | Variant Type | Level of Evidence Code | Variant Description |
|---|---|---|---|---|
| KRAS | COSM555 | SNV | 2 | p.Q61H |
| KRAS | COSM554 | SNV | 2 | p.Q61H |
| KRAS | COSM553 | SNV | 2 | p.Q61L |
| KRAS | COSM552 | SNV | 2 | p.Q61R |
| KRAS | COSM551 | SNV | 2 | p.Q61P |
| KRAS | COSM550 | SNV | 2 | p.Q61E |
| KRAS | COSM549 | SNV | 2 | p.Q61K |
| KRAS | COSM539 | SNV | 2 | p.G15D |
| KRAS | COSM538 | SNV | 2 | p.G15S |
| KRAS | COSM30567 | SNV | 2 | p.G13E |
| KRAS | COSM87280 | SNV | 2 | p.G13E |
| KRAS | COSM534 | SNV | 2 | p.G13V |
| KRAS | COSM533 | SNV | 2 | p.G13A |
| KRAS | COSM532 | SNV | 2 | p.G13D |
| KRAS | COSM527 | SNV | 2 | p.G13C |
| KRAS | COSM529 | SNV | 2 | p.G13R |
| KRAS | COSM528 | SNV | 2 | p.G13S |
| KRAS | COSM512 | SNV | 2 | p.G12F |
| KRAS | COSM514 | SNV | 2 | p.G12L |
| KRAS | COSM13643 | SNV | 2 | p.G12N |
| KRAS | COSM520 | SNV | 2 | p.G12V |
| KRAS | COSM522 | SNV | 2 | p.G12A |
| KRAS | COSM521 | SNV | 2 | p.G12D |
| KRAS | COSM516 | SNV | 2 | p.G12C |

| Gene Name | Variant ID | Variant Type | Level of Evidence Code | Variant Description |
|---|---|---|---|---|
| KRAS | COSM518 | SNV | 2 | p.G12R |
| KRAS | COSM517 | SNV | 2 | p.G12S |
| KRAS | COSM19404 | SNV | 3 | p. A146T |

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## Appendix II

## Patient Drug Information Handout and Wallet Card

### Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **copanlisib**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

**These are the things that you as a healthcare provider need to know:**

*Copanlisib interacts with certain specific enzymes in your liver and certain transport proteins that help move drugs in and out of cells.*

- The enzymes in question are **CYP3A4 and 1A1**. Copanlisib is broken down by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.
- The proteins in question are **P-gp, BCRP, and MATE2K**. Copanlisib is moved in and out of cells/organs by P-gp and BCRP. Copanlisib also inhibits MATE2K and may affect the clearance of other drugs that are dependent on this transport protein.

**<u>To the patient:</u> Take this paper with you to your medical appointments and keep the attached information card in your wallet.**

Copanlisib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

**These are the things that you and they need to know:**

Copanlisib must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **strong inducers/inhibitors of CYP3A4, 1A1, P-gp, and BCRP or substrates of MATE2K.**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is

_____

and he or she can be contacted at:

_____.

| **STUDY DRUG INFORMATION WALLET CARD** | |
|---|---|
| You are enrolled on a clinical trial using the experimental study drug **copanlisib.** This clinical trial is sponsored by the NCI. Copanlisib may interact with drugs that are processed by your liver or use certain transport proteins in your body. Because of this, it is very important to:<br>➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines.<br>➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.<br>➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement. | **Copanlisib** interacts with specific liver enzymes called CYP3A4 and 1A1, transport proteins P-gp, BCRP, and MATE2K, and must be used very carefully with other medicines that interact with these enzymes and transporters.<br>➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP3A4, 1A1, P-gp, and BCRP."** Copanlisib inhibits **"MATE2K"** and may affect how other medicines work in your body.<br>➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.<br>➢ Your study doctor's name is _____ and can be contacted at _____. |

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## Appendix III

## MANAGEMENT OF TRANSIENT GLUCOSE INCREASE ON THE DAY OF COPANLISIB INFUSION

| Criteria | Recommendation | Suggested Treatment |
|---|---|---|
| **Asymptomatic glucose increases ≤250mg/dL** | Does not generally require treatment with glucose lowering medication. | **None** |
| **Asymptomatic glucose increase > 250 mg/dl** | • Should have repeated laboratory glucose determination.<br>• 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.<br>• Consultation with endocrinologist is recommended | • Hydration if appropriate<br>• **When planning next infusion consider prophylaxis with oral glucose lowering medication** |
| **Symptomatic or persisting glucose increases>250mg/dL** | • Hydration status should be clinically assessed.<br>• If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV).<br>• 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.<br>• Prompt input from a diabetes specialist should be obtained. | • Hydration if appropriate<br>• Rapid/ short acting insulin may be given for glucose persisting at >250 mg/dL, or if the patient is symptomatic during the infusion day.<br>• Rapid/short acting insulin<br>• According to the institution sliding scale coverage of glucose persisting at >250 mg/dL is recommended, with oral or IV hydration as clinically appropriate<br>• **When planning next infusion consider prophylaxis with oral glucose lowering medication** |

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# Molecular Analysis for Therapy Choice (MATCH)
# MATCH Treatment Subprotocol Z1F: Copanlisib, PIK3CA

## Appendix IV

## DOSE MODIFICATION OF COPANLISIB FOR ARTERIAL HYPERTENSION

| Toxicity (CTCAE) | Study drug action | Recommendation |
|---|---|---|
| Pre-dose measurements<br>BP ≥150/90 mmHg | No dose should be given until recovery to < 150/90mmHg. | Consider BP lowering medication. Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to < 150/90mmHg. If BP doesn't return to < 150/90mmHg, delay dosing until next visit. |
| During infusion:<br>CTCAE hypertension of grade 3<br>or ≥160/100 mmHg | Infusion can be interrupted or slowed down and administration of BP lowering therapy should be initiated. | Infusion may be resumed when BP has returned to < 150/90mmHg at the investigator's discretion or skipped.<br>Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b] |
| Post-dose:<br>Drug-related<br>CTCAE hypertension of grade 3<br>or ≥160/100 mmHg [a] | – | Administration of BP lowering therapy should be initiated according to local standard of care.<br>Additional measurements to be performed as clinically indicated until recovery to <150/90mmHg.<br>Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b] |
| CTCAE hypertension of grade 4 | Permanent discontinuation | – |

CTCAE = Common Terminology Criteria for Adverse Events; BP = Blood pressure

[a] Not manageable despite optimal antihypertensive treatment.

[b] The lowest dose level is 30mg.