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

July 16, 2021

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 #29 to EAY131-Z1G, *MATCH Treatment Subprotocol Z1G: Phase II Study of Copanlisib in Patients with Tumors with PTEN Loss by IHC and any PTEN Sequencing Result*

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

The following revisions to the EAY131-Z1G protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Administrative edits made throughout document.
2.	Cover Page	Updated Version Date and addendum number.
3.	Cover Page	Replaced Dr. Fillip Janku, PhD as study “Subprotocol Chair” with Dr. Jordi Rodon, MD.
4.	Contacts Page	Replaced Dr. Fillip Janku, PhD contact information with Dr. Jordi Rodon, MD.
5.	Contacts Page	Revised “Michael Davies, MD” to “Michael Davies, MD, PhD”
6.	2.1.14	In third, bullet revised “Hb” to “Hgb”
7.	2.1.18	Revised template language regarding use of contraception while receiving treatment on study.

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	Section	Change
8.	3.3.2	Updated template language regarding “Second Primary Cancer Reporting Requirements”
9.	4	In footnote C, revised “women” to “patients”.

The following revisions to the EAY131-Z1G Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.

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

We request review and approval of this addendum to EAY131-Z1G so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

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

EAY131-Z1G

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Z1G: Phase II Study of Copanlisib in Patients with Tumors with PTEN Loss by IHC and any PTEN Sequencing Result

Rev. Add29

COPANLISIB TREATMENT SUBPROTOCOL CHAIR: Jordi Rodon, MD, PhD

COPANLISIB TREATMENT SUBPROTOCOL CO-CHAIR: Michael Davies, MD, PhD

Version Date: July 16, 2021

NOTE: This subprotocol (EAY131-Z1G) should be used in conjunction with the MATCH Master Protocol (EAY131).

SUBPROTOCOL ACTIVATION DATE

Incorporated in Addendum #13
Addendum #16
Addendum #22
Addendum #25
Addendum #29

Agent	IND#	NSC#	Supply
COPANLISIB	IND Sponsor: DCTD, NCI IND#:	784727	NCI Supplied

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Schema

Cycle = 28 days
Accrual Goal: 35

1. Introduction

1.1 PI3K/AKT/mTOR Pathway in Cancer

The PI3K/AKT/mTOR signaling pathway is one of the most frequently activated signaling cascades in cancer.[1,2] Class I PI3K is activated by a variety of signals, including many receptor tyrosine kinases (RTKs), cell-cell contacts, and activated RAS proteins, among others.[3] The activated PI3K phosphorylates phosphatidylinositols in the cell membrane at the 3'-OH position. These phospholipids interact with proteins that contain a pleckstrin homology (PH) domain, including the serine-threonine kinase AKT, also known as protein kinase B (PKB). Interactions of PH domain-containing proteins cause them to co-localize at the cell surface, where they often interact and activate each other (i.e. activation of AKT by phosphorylation of PDK1). The activated AKT acts on multiple effectors to regulate a number of key cellular functions, including angiogenesis, proliferation, survival, motility, and metabolism. PTEN, a lipid phosphatase that dephosphorylates phosphatidylinositols at the 3'OH position, is a critical negative regulator of PI3K activity.

The PI3K/AKT/mTOR signaling pathway is activated by many oncogenic events.[4,5] The PI3K/AKT/mTOR pathway is a key effector of activating oncogenic events that occur upstream of the pathway, including activating hotspot mutations (i.e EGFR) and gene amplifications (i.e. HER2/neu) affecting RTKs, and hotspot mutations in RAS family proteins (i.e. Kras). The pathway may also be activated by hotspot mutations in components of the pathway, including PIK3CA, AKT1, and AKT3. Signaling through the PI3K/AKT/mTOR signaling pathway can also be activated by loss of function of PTEN. Previous studies support that loss of PTEN function most commonly results from somatic mutations and gene deletions that cause loss of PTEN protein expression, with >95% loss of PTEN protein expression correlating with increased activation of AKT and other pathway effectors.[6-8] PTEN function can also be disrupted by mutations that disrupt the phosphatase domain of the PTEN protein, thus causing a loss of catalytic function.[9-11]

The high frequency of activation of the PI3K/AKT/mTOR signaling pathway in cancer makes it an attractive target for therapeutic development. In particular, there is a strong rationale to test the hypothesis that agents that inhibit the pathway will achieve clinical benefit in patients with alterations in the pathway itself, particularly PIK3CA mutations and PTEN loss.[12] However, preclinical data suggest that different oncogenic events in this pathway (i.e. PIK3CA mutations and PTEN loss) may have different functional consequences, a hypothesis that is further supported by the frequently observed overlap of mutations of this pathway in tumors.[12-14] Thus, this protocol is designed to specifically test the hypothesis that complete loss of PTEN protein expression will predict clinical benefit from treatment with the pan-PI3K inhibitor copanlisib in patients without PIK3CA mutations.

1.2 Copanlisib

Copanlisib (BAY 80-6946) is a novel, highly selective, pan-class phosphatidylinositol 3-kinase (PI3K) inhibitor with potent activity against both the δ and α isoforms. A summary of the available relevant non-clinical and clinical

data is provided below. Study details and additional information can be found in the Investigator Brochure.

1.2.1 Preclinical Data

The pharmacodynamic effects of copanlisib have been characterized extensively in preclinical cancer models, including cell lines and xenografts with loss of PTEN (see Investigator Brochure for detailed description of results). In enzymatic assays, copanlisib inhibited all PI3K isoforms with single digit nanomolar IC50, whereas no significant activity was seen against a panel of 220 other kinases, except mTOR (IC50 45 nM). Further testing supports a 100- to 1000-fold cellular selectivity for inhibition of PI3K versus mTOR signaling by copanlisib. Inhibition of both AKT activation and cell proliferation *in vitro* was achieved with copanlisib treatment in cancer cell lines of multiple types, including several with PTEN loss (Investigator Brochure, Table 4-4 and Figure 4-1, and Liu et al., 2013).[15]

In vivo preclinical testing also demonstrated efficacy in multiple cancer xenograft models. Notably, partial tumor regression was observed in the U87 glioblastoma model, which has loss of PTEN function due to an in-frame PTEN deletion that results in a truncated protein.[9]

1.2.2 Clinical Data

As of Feb 01, 2016, 627 patients with advanced cancer have been treated across eight phase 1, three phase 2 and three phase 3 studies. Copanlisib has also been studied in healthy volunteers

1.2.3 Pharmacodynamics:

The PD effects on glucose and plasma insulin levels as well as 18[F]FDG-CT/PET have been investigated in the first-in-man Study 12871 using copanlisib monotherapy at different doses. 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, i.e., not observed after copanlisib treatment had been permanently discontinued. Dose-related increases in glucose and insulin as well as copanlisib exposure-related increases in plasma glucose were observed. Plasma insulin increase to greater than 2 times the baseline value was reported in 90% of the patients, starting at the 0.2 mg/kg dose level. 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. Paired FDG-PET scans were available in 21 patients. Between baseline and Cycle 1 Day 3 or Cycle 1 Day 4, 7 patients (33%) showed a reduction of more than 25% in FDG uptake. There was a weak correlation between changes in maximum standard uptake value (maximum standard uptake value [SUVmax]) and AUC(0-25) of copanlisib.

1.2.4 Pharmacokinetics:

Copanlisib (BAY 80-6946) PK have been characterized in the following studies in cancer patients: (i) single agent dose escalation study in cancer patients in the US (Study 12871), (ii) a dose escalation study in combination with refametinib (BAY 86-9766) in the US and Europe (Study 12876), (iii) a single agent dose escalation study in cancer patients in Japan (Study 15205), in two studies in combination with chemotherapy, either with paclitaxel (Study 12874), or with gemcitabine and gemcitabine/cisplatin (Study 12875). Furthermore, Study 16790 a PD study with copanlisib as monotherapy in patients with NHL and solid tumors as well as a Study 16270 to evaluate potential drug-drug interaction of copanlisib with itraconazole (a strong CYP3A4 inhibitor) and rifampin (a strong CYP3A4 inducer) are ongoing. Results on single agent studies is summarized below. Please refer to the IB for pharmacokinetics of copanlisib in combination with other drugs.

In Study 12871, copanlisib PK were characterized on Cycle 1 Day 1 and 15 and Cycle 3 Day 15. In general, PK data indicate similar copanlisib Cmax and AUC(0-25) on Day 1 and Day 15, indicating lack of significant accumulation after once weekly administration. Dose proportional increase in copanlisib exposure (Cmax and AUC(0-25)) was observed between 0.1 mg/kg to 1.2 mg/kg with moderate to high inter-subject variability. At the MTD of 0.8 mg/kg (n=28), the geometric mean copanlisib terminal phase t1/2 was 38.2 hours (CV: 42.5%), which supports once weekly dosing. 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.

In Study 15205, copanlisib doses of 0.4 mg/kg and 0.8 mg/kg were evaluated in Japanese patients. Pharmacokinetic results at the 0.4 and 0.8 mg/kg dose level indicate generally comparable (slightly lower) exposure in Japanese patients and non-Japanese patients enrolled in the US Study 12871.

Study 16270 is an ongoing 2 armed Phase 1 study aims to evaluate the effect of itraconazole (a strong CYP3A4 inhibitor) or rifampin (a strong CYP3A4 inducer) on the PK of single i.v. doses of copanlisib and evaluates parameters of cardiac safety in patients with advanced solid tumors. Cycle duration is 4 weeks. Arm A evaluates the effect of itraconazole on copanlisib PK. Arm B evaluates the effect of rifampin on copanlisib PK and the effect of copanlisib on QTc and left ventricular ejection fraction (LVEF).

The PK of copanlisib were characterized after a 1 hour i.v. infusion administered once weekly. In the dose escalation cohorts, serial PK samples were collected on Cycle 1 Day 1 (up to 48 hours after end of infusion at dose levels ≤ 0.2 mg/kg and approximately 168 hours after the start of infusion at dose levels > 0.2 mg/kg) and Cycle 1 Day 15 (up to 24 hours after the end of infusion). In general, PK data indicate similar copanlisib Cmax and AUC(0-25) on Day 1 and Day 15, indicating lack of significant accumulation after once weekly

administration. Nearly dose proportional increase in copanlisib exposure (Cmax and AUC(0-25)) was observed between 0.1 mg/kg to 1.2 mg/kg with moderate to high inter-subject variability. In the MTD expansion cohort, serial PK samples were collected on Cycle 1 Day 1 and 15 and Cycle 3 Day 15 (up to 8 hours after the end of infusion). At the MTD of 0.8 mg/kg, Cycle 1 Day 1, geometric mean (n=41) Cmax was 454)g/L and AUC(0-tlast), exposure covering the 1-week dosing interval, was 2880)g•h/L. Inter-patient variability in copanlisib Cmax and AUC(0-tlast) at 0.8 mg/kg was high with values of 73.3% CV for Cmax and about 46.5% for AUC(0-tlast). The geometric mean copanlisib terminal phase t1/2 was 38.2 hours (CV: 42.5%), which supports once weekly dosing. Reliable terminal t1/2 could only be calculated in 28 patients. After administration of 0.4 mg/kg copanlisib to 6 diabetic patients, geometric mean Cmax was 138)g/L (CV: 36.7%) on Cycle 1 Day 1 and 151)g/L (CV: 23.4%) on Cycle 1 Day 15. Geometric mean AUC(0-25) was 607)g0hour/L (CV: 43.6%) on Cycle 1 Day 1 and 687)g0hour/L (CV: 36.0%) on Cycle 1 Day 15. Inter-subject variability for copanlisib Cmax and AUC(0-25) was moderate to high and similar to variability in other cohorts with PK parameters varying by a factor of about 3. Applying a adjusted body weight dosing, AUC(0-25) values on Cycle 1 Day 1 in obese patients were similar to AUC(0-25) values of other patients with normal BMI (130 mg/m2).

1.2.5 Distribution

Plasma protein binding of copanlisib was determined in vitro with a free fraction of 15.8% in human plasma. Similar protein binding of the M-1 metabolite was observed with the free fraction of 20%.

1.2.6 Metabolism

In vitro, oxidation, dehydrogenation, and dealkylation reactions were identified as the major oxidative pathways in liver microsomes and hepatocytes of different animal species and human. Based on in vitro experiments, CYP3A4 is the major metabolizing enzyme, while CYP1A1 also contributes to a minor extent.

1.2.7 Elimination

In Study 12871, copanlisib at the MTD (0.8 mg/kg was eliminated from plasma with a geometric mean of 38.2 hours (CV: 42.5%). Copanlisib is excreted in feces and urine as unchanged drug and metabolites.

1.3 Safety

The relationship between individual random effects on clearance and selected covariates body weight, age, BMI, BSA, LBM, race, and sex on CL was explored across studies. Formal covariate analysis confirmed that there is no statistically significant ($p < 0.001$) correlation between clearance and any of the selected covariates. Based on the lack of significant impact of body weight and other covariates on clearance of copanlisib a flat dose regimen of 60 mg weekly on a 3 week on, one week off was recommended for future studies.

Based on pre-clinical data, copanlisib began testing in a phase 1 dose escalation first in human study, 12871 in patients with advanced cancers. A dose of 0.8mg/kg was determined to be the maximum tolerated dose in non-diabetic patients. Dose limiting toxicity was acute hypertension at 0.4mg/kg in one patient and left ventricular systolic dysfunction with ischemic EKG changes and lactic acidosis at 1.2 mg/kg in another patient consistent with safety studies in dogs. Increased BP was frequently observed within the first 3 hours of infusion which needed antihypertensive therapy. Adverse events noted in more than 20% of patients include hyperglycemia (63.2%), nausea (38.6%) and hypertension (21.1%). Most common grade 3 AE but regardless of seriousness and causality, occurring in >5% of the 57 patients were: hyperglycemia (33.3%), hypertension (19.3%), anemia (7.0%) and AST increased (5.3%). Three Follicular Lymphoma patients experienced any treatment-emergent interstitial pneumonitis, all with a severity of Grade 3 and assessed as serious. Of note, no pneumonitis was reported in the 48 patients with solid tumors treated in this study. Study 16790 is a phase 1 PD study to evaluate effects of PD biomarkers in patients with NHL and selected solid tumors at 2 dose levels, 0.4mg/kg and 0.8 mg/kg. Diabetic patients are allowed to be treated on 2 cohorts in this study at a flat dose of 45 mg and 60mg and only one patient has been treated so far. Most common TEAEs of any grade occurring in more than 20% of patients on study 16790 were hyperglycemia and fatigue (37.5%), hypertension (33%), anemia and nausea (25%), as well as diarrhea (20.8%). This study is ongoing and PTEN or PI3K mutation status is unknown at this time. Three phase 1 studies, (12874, 12875 and 1276) are ongoing which were done to determine MTD of copanlisib in combination with paclitaxel, gemcitabine+ cisplatin and refametinib (MEK inhibitor). Study 16270 is evaluating potential drug interactions of copanlisib with itraconazole (a strong CYP3A4 inhibitor) and rifampin (a strong CYP3A4 inducer). A healthy volunteer study, 16353 was completed with a dose of 12 mg of copanlisib and was well tolerated. Study 15205 is a single agent dose escalation study in 10 Japanese patients with advanced solid tumors. In this study, PK samples were collected from 3 Japanese patients at the 0.4 mg/kg dose level and seven patients at the 0.8 mg/kg dose level. Exposures of copanlisib increased in a roughly dose proportional manner. The plasma concentration-time profiles were similar between Japanese and non-Japanese patients at both the 0.4 mg/kg and 0.8 mg/kg dose level. Treatment emergent AE of all grade in more than 20% of patients in study 16349 which is limited to non-Hodgkin's lymphoma included hyperglycemia (56.8%), hypertension (53.1%), diarrhea (33.3%), neutropenia (23.5%), and fatigue (21.0%). Hyperglycemia peaked 5 to 8 hours after treatment and was reversible. This is an expected on target effect as PI3K is required for downstream signaling from the insulin receptor. Inhibition of this pathway leads to impaired uptake of glucose with a reactive rise in plasma insulin and glucose levels.

1.4 Efficacy

The data so far from copanlisib trials in lymphoma imply that low or total loss of PTEN expression predicts for response. Expansion of study 12871 in lymphomas showed 6 PRs and 1 CR among 9 patients treated. Four of six patients with null or low (< 5%) PTEN expression by IHC had a response (66%) whereas only 15% of patients with higher PTEN expression by IHC responded (Bayer data). There is not as much data available for solid tumors, but the latest data is from the expansion of study 12871 in 25 solid tumors. One patient with

endometrial cancer had a complete response, and she had PTEN loss by IHC, as well as PTEN and PIK3CA mutations. Two patients with extended stable disease also had PTEN loss by IHC. Due to the small number of patients with solid tumors entered, and the very few responses in these patients, we have very little data on the relationship of PTEN loss to response rate with this agent. However, the data that do exist conform to our level of evidence 3: at least one patient with PTEN loss by IHC responded to copanlisib with solid tumors (and several did so with lymphomas).

Out of 46 patients in study 16790 clinical benefit rate (CR, PR or SD) was seen in 38% of patients with solid tumors. Interestingly, all 6 patients with follicular lymphoma experienced an objective response. One patient is still on treatment for over 3 years now. On exploratory analysis of the lymphoma patients, one patient had complete PTEN loss and four patients had low PTEN (1-5 % staining of tumor cells).

Based on this a phase 2 study, 16349 was undertaken. 29 out of 32 patients with indolent lymphoma had a clinical benefit rate with an objective response rate of 44%. Among patients with aggressive lymphomas, 20 out of 46 patients had a clinical benefit with an objective response rate of 26%. Analysis of PTEN and mutations in study 12871 showed about 50% of solid tumors had complete loss of PTEN by IHC. Copanlisib is being tested in combination with chemotherapy in studies 12874, 12875 and 12876 and 2 patients in study 12875 with complete loss of PTEN achieved partial response or prolonged disease stabilization. Multiple phase 2 and 3 studies have been launched in Non-Hodgkin's lymphoma but none of the studies require tumors to have PI3K mutations or PTEN loss by IHC. Based on our data the anticipated response rate should be around 20% (Janku et al. Cell Rep 2014).

Complete loss of PTEN by IHC is rarer than mutation in PTEN. We have already accrued an arm that had complete loss of expression of PTEN by IHC in a time period of less than one year. We have quite a few PTEN losses that have been screened while arm P has been closed, and these patients, if their biopsy occurred < 5 months previously, would be offered participation in this arm. MATCH is now in the "rare variant initiative" and is not screening biopsies currently. Rather, patients can enter MATCH with results from an outside assay. If a patient has a PTEN mutation, their archived specimen will be assayed by IHC for PTEN expression in order to be able to assign them to arm Z1G or Z1H, along with the results of the outside assay.

This arm has some overlap with Arm Z1F, which will allow patients with PTEN loss to enroll, but Z1G and Z1H do not allow patients with PIK3CA mutation. If patients have both a PIK3CA mutation and PTEN IHC loss, patients will be assigned to Z1F. Arms Z1F, Z1H, and Z1G will provide complementary information as there are very likely to be patients in Z1F with PIK3CA mutation but PTEN intact; PIK3CA mutation with loss of PTEN expression and PIK3CA mutation with PTEN mutations but retained expression of PTEN by IHC (the latter two conditions occur in half or less of patients, depending on tumor types enrolled). However, the arms Z1H and Z1G will only have patients with PTEN loss or mutation. We will thus get a signal as to whether the agent is active when there are coexisting abnormalities in PTEN and PIK3CA, PIK3CA abnormalities alone, or PTEN abnormalities alone (as well as if expression of PTEN is null).

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 complete loss of cytoplasmic and nuclear PTEN by immunohistochemistry as determined via the MATCH Master Protocol and described in Appendix I. Patients can have any PTEN mutation or deletion status, but MUST have PTEN loss by IHC.

NOTE: For patients entering the study, all patients must have PTEN IHC performed as described in the MATCH Master Protocol. This includes patients entering the study via the outside assay process (Appendix XIV of the MATCH Master Protocol).

_____ 2.1.3 Patients must not have co-existing aberrations in the MAPK or PI3K/MTOR pathways as determined by the MATCH screening assessment in NRAS, HRAS, KRAS, BRAF, PIK3CA, AKT or mTOR. See Appendix I for the corresponding Levels of Evidence.

_____ 2.1.4 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: _____

_____ 2.1.5 Patients must not have known hypersensitivity to copanlisib or compounds of similar chemical or biologic composition.

_____ 2.1.6 Patients must not have had prior treatment with copanlisib or other PI3K inhibitors, AKT inhibitors or mTOR inhibitors.

_____2.1.7 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.

_____ 2.1.8 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 _____ 2.1.9 Patients with Type I or II diabetes mellitus must have a HbA1c ≤ 8.5% within 28 days from registration.

_____ 2.1.10 Patients must not have uncontrolled hypertension defined as SBP greater than 160 mmHg or diastolic BP greater than 100 mmHg or use of more than 2 anti-hypertensive medications.

_____ 2.1.11 Patients must not have HER2 positive (3+ by IHC or FISH ratio ≥ 2) breast cancer.

_____ 2.1.12 Patients must not have indolent NHL (Non-Hodgkin's Lymphoma) or DLBCL (diffuse large B cell lymphoma) because other studies are ongoing with this agent in this group patients.

_____ 2.1.13 Patients must not be on anti-arrhythmic therapy other than digoxin or beta-blockers.

Rev. Add16 _____2.1.14 Patients must have adequate marrow function as defined below:

- ANC ≥ $1.5x10^9$ /L
- Platelets ≥$100x10^9$ /L

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- Hgb > 9 g/dl

Rev. Add16 _____ 2.1.15 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 _____ 2.1.16 Patients with non-healing wound, ulcer, or bone fracture are not eligible.

Rev. Add16 _____ 2.1.17 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.

Rev. Add29

_____ 2.1.18 Patients must agree not to conceive or father children by agreeing 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
Rev. Add25

Pre-dose glucose levels

Period	Pre-dose glucose levels
Day 1 of cycle 1	< 160 mg/dL (fasting) < 200 mg/dL (non-fasting)
Day 1 of subsequent cycles	< 160 mg/dL (fasting) < 200 mg/dL (non-fasting)
Days 8 and 15 of each cycle	< 160 mg/dL (fasting) < 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 (finger stick or serum glucose) is required before each copanlisib infusion. The glucose testing is scheduled as follows:

- On Cycle 1 Day 1: Glucose test is performed before starting copanlisib IV infusion at time 0 hour and at the end of the infusion (1 hour after starting infusion).
- On all subsequent infusion days: Glucose test is performed before starting copanlisib IV infusion. Post-dose glucose monitoring after C1D1 may be performed as clinically indicated at the investigator's discretion.

  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 subprotocols 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 Z1G

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.

Rev. Add25

EAY131 – Subprotocol Z1G 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 female patient is on copanlisib, or within 28 days of the female patient'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 Z1G specific expedited reporting exceptions:

For Subprotocol Z1G, 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.

Rev. Add29

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 as follows:

- **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 on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

     NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).
  3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
  4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.

5. 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 Event 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 via CTEP-AERS (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			

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%)**	
	Muscle cramp		***Muscle cramp (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis[3]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythroderma	
		Pruritus	
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 2)***

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Eosinophilia

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

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

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

IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder

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

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

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

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

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

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

PSYCHIATRIC DISORDERS - Confusion

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

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

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

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

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

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 < 200 mg/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 ≤ 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]). Consider dermatological consultation. Consider obtaining photographs of rash if permitted by local regulations.	Hold all study treatment until Grade ≤ 1. For Grade 3, restart copanlisib at the next lower dose upon discussion with Overall Principal Investigator, or permanently discontinue treatment. 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 copanlsisib 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.

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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: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤ 150 mmHg and DBP ≤ 90 mmHg in two separate readings during up to three subsequent visits. - 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. - Asymptomatic hypertension: SBP > 150 mmHg and/or DBP > 90 mmHg in the absence of the above symptoms.		
(Scenario A) • Asymptomatic and persistent SBP of ≥ 150 and < 160 mmHg, or DBP ≥ 90 and < 100 mmHg, OR • Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • 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) • Asymptomatic SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg, OR • Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt copanlisib. • Once BP is well-controlled, restart copanlisib at a reduced dose.
(Scenario C) • Symptomatic hypertension OR • 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). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended. • Continue follow-up per protocol.	• Discontinue copanlisib
(Scenario D) • 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 Resume at 60 mg after recovery to ≤ grade 1 Recurrence at 60 mg: Hold Copanlisib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Hold Copanlisib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Discontinue Copanlisib
Grade 3	Hold Copanlisib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Hold Copanlisib Resume at 30 mg after recovery to ≤ grade 1 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.

Rev. Add16

4. Study Parameters

4.1 Therapeutic Parameters for CopanlisibTreatment

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 ,including 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.”

Rev. Add29 C. Blood pregnancy test (patients 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:

- For patients entering the study via the outside assay process (Appendix XIV of the MATCH Master Protocol), central IHC testing by the MD Anderson MATCH trial laboratory confirming expression of PTEN is required prior to receiving treatment assignment.
- 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 timepoint: 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 2.1.9.

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.

Rev. Add16

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.

Rev. Add16

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.

Rev. Add16

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

1. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. Cell, 144(5), 646-674. doi: 10.1016/j.cell.2011.02.013
2. Millis, S. Z., Ikeda, S., Reddy, S., Gatalica, Z., & Kurzrock, R. (2016). Landscape of phosphatidylinositol-3-kinase pathway alterations across 19 784 diverse solid tumors. JAMA Oncology. doi: 10.1001/jamaoncol.2016.0891
3. Davies, M. A. (2011). Regulation, Role, and Targeting of Akt in Cancer. J Clin Oncol, 29(35), 4715-4717. doi: JCO.2011.37.4751 [pii]10.1200/JCO.2011.37.4751
4. Thorpe, L. M., Yuzugullu, H., & Zhao, J. J. (2015). PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer, 15(1), 7-24. doi: 10.1038/nrc3860
5. Vanhaesebroeck, B., Stephens, L., & Hawkins, P. (2012). PI3K signalling: the path to discovery and understanding. Nat Rev Mol Cell Biol, 13(3), 195-203.
6. Bucheit, A. D., Chen, G., Siroy, A., Tetzlaff, M., Broaddus, R., Milton, D., Davies, M. A., et al. (2014). Complete loss of PTEN protein expression correlates with shorter time to brain metastasis and survival in stage IIIB/C melanoma patients with BRAFV600 mutations. Clin Cancer Res, 20(21), 5527-5536. doi: 10.1158/1078-0432.CCR-14-1027

   \1078-0432.CCR-14-1027 [pii]
7. Djordjevic, B., Hennessy, B. T., Li, J., Barkoh, B. A., Luthra, R., Mills, G. B., & Broaddus, R. R. (2012). Clinical assessment of PTEN loss in endometrial carcinoma: immunohistochemistry outperforms gene sequencing. Mod Pathol, 25(5), 699-708.
8. Roszik, J., Wu, C.-J., Siroy, A. E., Lazar, A. J., Davies, M. A., Woodman, S. E., & Kwong, L. N. (2016). Somatic Copy Number Alterations at Oncogenic Loci Show Diverse Correlations with Gene Expression. Scientific Reports, 6, 19649. doi: 10.1038/srep19649
9. Furnari, F. B., Lin, H., Huang, H. J. S., & Cavenee, W. K. (1997). Growth suppression of glioma cells by PTEN requires a functional phosphatase catalytic domain. Proceedings of the National Academy of Sciences of the United States of America, 94(23), 12479-12484.
10. Han, S.-Y., Kato, H., Kato, S., Suzuki, T., Shibata, H., Ishii, S., . . . Ishioka, C. (2000). Functional Evaluation of PTEN Missense Mutations Using in Vitro Phosphoinositide Phosphatase Assay. Cancer Research, 60(12), 3147-3151.
11. Rodríguez-Escudero, I., Oliver, M. D., Andrés-Pons, A., Molina, M., Cid, V. J., & Pulido, R. (2011). A comprehensive functional analysis of PTEN mutations: implications in tumor- and autism-related syndromes. Human Molecular Genetics, 20(21), 4132-4142. doi: 10.1093/hmg/ddr337
12. Janku, F., Hong, David S., Fu, S., Piha-Paul, Sarina A., Naing, A., Falchook, Gerald S., Kurzrock, R. (2014). Assessing PIK3CA and PTEN in Early-Phase Trials with PI3K/AKT/mTOR Inhibitors. Cell Reports, 6(2), 377-387. doi: http://dx.doi.org/10.1016/j.celrep.2013.12.035

13. Stemke-Hale, K., Gonzalez-Angulo, A. M., Lluch, A., Neve, R. M., Kuo, W. L., Davies, M., Hennessy, B. T. (2008). An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. Cancer Res, 68(15), 6084-6091. doi: 68/15/6084 [pii] 10.1158/0008-5472.CAN-07-6854

14. Vasudevan, K. M., Barbie, D. A., Davies, M. A., Rabinovsky, R., McNear, C. J., Kim, J. J., Garraway, L. A. (2009). AKT-independent signaling downstream of oncogenic PIK3CA mutations in human cancer. Cancer Cell, 16(1), 21-32. doi: S1535-6108(09)00177-9 [pii] 10.1016/j.ccr.2009.04.012

15. Liu, N., Rowley, B. R., Bull, C. O., Schneider, C., Haegebarth, A., Schatz, C. A., . . . Ziegelbauer, K. (2013). BAY 80-6946 Is a Highly Selective Intravenous PI3K Inhibitor with Potent p110α and p110δ Activities in Tumor Cell Lines and Xenograft Models. Molecular Cancer Therapeutics, 12(11), 2319-2330. doi: 10.1158/1535-7163.mct-12-0993-t

Copanlisib
Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1G: Copanlisib, PTEN Loss

Appendix I

Actionable Mutation for Sub-Protocol EAY131-Z1G is PTEN Loss on IHC.

Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
NRAS	COSM585	SNV	p.Q61H	2
NRAS	COSM586	SNV	p.Q61H	2
NRAS	COSM583	SNV	p.Q61L	2
NRAS	COSM584	SNV	p.Q61R	2
NRAS	COSM582	SNV	p.Q61P	2
NRAS	COSM581	SNV	p.Q61E	2
NRAS	COSM580	SNV	p.Q61K	2
NRAS	COSM574	SNV	p.G13V	2
NRAS	COSM575	SNV	p.G13A	2
NRAS	COSM573	SNV	p.G13D	2
NRAS	COSM570	SNV	p.G13C	2
NRAS	COSM569	SNV	p.G13R	2
NRAS	COSM571	SNV	p.G13S	2
NRAS	COSM566	SNV	p.G12V	2
NRAS	COSM565	SNV	p.G12A	2
NRAS	COSM564	SNV	p.G12D	2
NRAS	COSM562	SNV	p.G12C	2
NRAS	COSM561	SNV	p.G12R	2
NRAS	COSM563	SNV	p.G12S	2
HRAS	COSM502	SNV	p.Q61H	2
HRAS	COSM503	SNV	p.Q61H	2
HRAS	COSM498	SNV	p.Q61L	2
HRAS	COSM499	SNV	p.Q61R	2
HRAS	COSM500	SNV	p.Q61P	2
HRAS	COSM497	SNV	p.Q61E	2
HRAS	COSM496	SNV	p.Q61K	2
HRAS	COSM489	SNV	p.G13V	2
HRAS	COSM490	SNV	p.G13D	2
HRAS	COSM488	SNV	p.G13C	2
HRAS	COSM486	SNV	p.G13R	2

Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
HRAS	COSM487	SNV	p.G13S	2
HRAS	COSM483	SNV	p.G12V	2
HRAS	COSM485	SNV	p.G12A	2
HRAS	COSM484	SNV	p.G12D	2
HRAS	COSM481	SNV	p.G12C	2
HRAS	COSM482	SNV	p.G12R	2
HRAS	COSM480	SNV	p.G12S	2
KRAS	COSM555	SNV	p.Q61H	2
KRAS	COSM554	SNV	p.Q61H	2
KRAS	COSM553	SNV	p.Q61L	2
KRAS	COSM552	SNV	p.Q61R	2
KRAS	COSM551	SNV	p.Q61P	2
KRAS	COSM550	SNV	p.Q61E	2
KRAS	COSM549	SNV	p.Q61K	2
KRAS	COSM539	SNV	p.G15D	2
KRAS	COSM538	SNV	p.G15S	2
KRAS	COSM30567	SNV	p.G13E	2
KRAS	COSM87280	SNV	p.G13E	2
KRAS	COSM534	SNV	p.G13V	2
KRAS	COSM533	SNV	p.G13A	2
KRAS	COSM532	SNV	p.G13D	2
KRAS	COSM527	SNV	p.G13C	2
KRAS	COSM529	SNV	p.G13R	2
KRAS	COSM528	SNV	p.G13S	2
KRAS	COSM512	SNV	p.G12F	2
KRAS	COSM514	SNV	p.G12L	2
KRAS	COSM13643	SNV	p.G12N	2
KRAS	COSM520	SNV	p.G12V	2
KRAS	COSM522	SNV	p.G12A	2
KRAS	COSM521	SNV	p.G12D	2
KRAS	COSM516	SNV	p.G12C	2
KRAS	COSM518	SNV	p.G12R	2
KRAS	COSM517	SNV	p.G12S	2
KRAS	COSM19404	SNV	p. A146T	3
BRAF	COSM1127	SNV	p.V600R	**2**
BRAF	COSM1583011	SNV	p.V600R	2
BRAF	COSM308550	SNV	p.V600D	2

Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
BRAF	COSM473	SNV	p.V600K	1
BRAF	COSM474	SNV	p.V600R	2
BRAF	COSM476	SNV	p.V600E	1
BRAF	COSM477	SNV	p.V600D	2
BRAF	AGTRAP-BRAF.A5B8.COSF828	Fusion	AGTRAP-BRAF.A5B8.COSF828	3
BRAF	AKAP9-BRAF.A8B9.COSF1013	Fusion	AKAP9-BRAF.A8B9.COSF1013	3
BRAF	CDC27-BRAF.C16B9	Fusion	CDC27-BRAF.C16B9	3
BRAF	FAM131B-BRAF.F2B9.COSF1189	Fusion	FAM131B-BRAF.F2B9.COSF1189	3
BRAF	FCHSD1-BRAF.F13B9.COSF404	Fusion	FCHSD1-BRAF.F13B9.COSF404	3
BRAF	KIAA1549-BRAF.K16B11	Fusion	KIAA1549-BRAF.K16B11	3
BRAF	KIAA1549-BRAF.K16B9	Fusion	KIAA1549-BRAF.K16B9	3
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	KIAA1549-BRAF.K17B10.COSF509	3
BRAF	KIAA1549-BRAF.K18B10	Fusion	KIAA1549-BRAF.K18B10	3
BRAF	KIAA1549-BRAF.K19B9	Fusion	KIAA1549-BRAF.K19B9	3
BRAF	PAPSS1-BRAF.P5B9	Fusion	PAPSS1-BRAF.P5B9	3
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	SLC45A3-BRAF.S1B8.COSF871	3
BRAF	SND1-BRAF.S16B9	Fusion	SND1-BRAF.S16B9	3
BRAF	TAX1BP1-BRAF.T8B11	Fusion	TAX1BP1-BRAF.T8B11	3
BRAF	TRIM24-BRAF.T9B9	Fusion	TRIM24-BRAF.T9B9	3
BRAF	AGAP3-BRAF.A10B11	Fusion	AGAP3-BRAF.A10B11	3
BRAF	AGAP3-BRAF.A9B9	Fusion	AGAP3-BRAF.A9B9	3
BRAF	AGK-BRAF.A2B8	Fusion	AGK-BRAF.A2B8	3
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	Fusion	AGTRAP-BRAF.A5B8.COSF828.1	3
BRAF	AKAP9-BRAF.A21B10	Fusion	AKAP9-BRAF.A21B10	3
BRAF	AKAP9-BRAF.A22B9	Fusion	AKAP9-BRAF.A22B9	3
BRAF	AKAP9-BRAF.A28B9	Fusion	AKAP9-BRAF.A28B9	3
BRAF	AKAP9-BRAF.A7B11	Fusion	AKAP9-BRAF.A7B11	3
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	Fusion	AKAP9-BRAF.A8B9.COSF1013.1	3
BRAF	AP3B1-BRAF.A22B9	Fusion	AP3B1-BRAF.A22B9	3
BRAF	ARMC10-BRAF.A4B11	Fusion	ARMC10-BRAF.A4B11	3
BRAF	ATG7-BRAF.A18B9	Fusion	ATG7-BRAF.A18B9	3

Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
BRAF	BAIAP2L1-BRAF.B12B9	Fusion	BAIAP2L1-BRAF.B12B9	3
BRAF	BBS9-BRAF.B19B4	Fusion	BBS9-BRAF.B19B4	3
BRAF	BCL2L11-BRAF.B3B10	Fusion	BCL2L11-BRAF.B3B10	3
BRAF	BRAF-AP3B1.B8A23	Fusion	BRAF-AP3B1.B8A23	3
BRAF	BRAF-CIITA.B9C6	Fusion	BRAF-CIITA.B9C6	3
BRAF	BRAF-MACF1.B8M15	Fusion	BRAF-MACF1.B8M15	3
BRAF	BRAF-MRPS33.B1M2	Fusion	BRAF-MRPS33.B1M2	3
BRAF	BRAF-SLC26A4.B3S7	Fusion	BRAF-SLC26A4.B3S7	3
BRAF	BRAF-SUGCT.B1S13	Fusion	BRAF-SUGCT.B1S13	3
BRAF	BTF3L4-BRAF.B3B11	Fusion	BTF3L4-BRAF.B3B11	3
BRAF	C7orf73-BRAF.C2B9	Fusion	C7orf73-BRAF.C2B9	3
BRAF	CCDC6-BRAF.C1B9	Fusion	CCDC6-BRAF.C1B9	3
BRAF	CCDC91-BRAF.C11B9	Fusion	CCDC91-BRAF.C11B9	3
BRAF	CCNY-BRAF.C1B10	Fusion	CCNY-BRAF.C1B10	3
BRAF	CDC27-BRAF.C16B9.1	Fusion	CDC27-BRAF.C16B9.1	3
BRAF	CEP89-BRAF.C16B9	Fusion	CEP89-BRAF.C16B9	3
BRAF	CLCN6-BRAF.C2B11.COSF1440	Fusion	CLCN6-BRAF.C2B11.COSF1440	3
BRAF	CLIP2-BRAF.C6B11	Fusion	CLIP2-BRAF.C6B11	3
BRAF	CUL1-BRAF.C7B9	Fusion	CUL1-BRAF.C7B9	3
BRAF	CUX1-BRAF.C10B9	Fusion	CUX1-BRAF.C10B9	3
BRAF	DYNC1I2-BRAF.D7B10	Fusion	DYNC1I2-BRAF.D7B10	3
BRAF	EML4-BRAF.E6B10	Fusion	EML4-BRAF.E6B10	3
BRAF	EPS15-BRAF.E22B10	Fusion	EPS15-BRAF.E22B10	3
BRAF	ERC1-BRAF.E12B10	Fusion	ERC1-BRAF.E12B10	3
BRAF	ERC1-BRAF.E17B8	Fusion	ERC1-BRAF.E17B8	3
BRAF	FAM114A2-BRAF.F9B11	Fusion	FAM114A2-BRAF.F9B11	3
BRAF	FAM131B-BRAF.F1B10.COSF1191	Fusion	FAM131B-BRAF.F1B10.COSF1191	3
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	Fusion	FAM131B-BRAF.F2B9.COSF1189.1	3
BRAF	FAM131B-BRAF.F3B9.COSF1193	Fusion	FAM131B-BRAF.F3B9.COSF1193	3
BRAF	FCHSD1-BRAF.F13B9.COSF403	Fusion	FCHSD1-BRAF.F13B9.COSF403	3
BRAF	FXR1-BRAF.F13B10	Fusion	FXR1-BRAF.F13B10	3
BRAF	GATM-BRAF.G2B11	Fusion	GATM-BRAF.G2B11	3
BRAF	GHR-BRAF.G1B10	Fusion	GHR-BRAF.G1B10	3
BRAF	GNAI1-	Fusion	GNAI1-	3

Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
	BRAF.G1B10.COSF1442		BRAF.G1B10.COSF1442	
BRAF	GTF2I-BRAF.G4B10	Fusion	GTF2I-BRAF.G4B10	3
BRAF	HERPUD1-BRAF.H4B7	Fusion	HERPUD1-BRAF.H4B7	3
BRAF	KCTD7-BRAF.K3B8	Fusion	KCTD7-BRAF.K3B8	3
BRAF	KCTD7-BRAF.K4B8	Fusion	KCTD7-BRAF.K4B8	3
BRAF	KDM7A-BRAF.K11B11	Fusion	KDM7A-BRAF.K11B11	3
BRAF	KIAA1549-BRAF.K12B11	Fusion	KIAA1549-BRAF.K12B11	3
BRAF	KIAA1549-BRAF.K12B9.COSF1474	Fusion	KIAA1549-BRAF.K12B9.COSF1474	3
BRAF	KIAA1549-BRAF.K13B9	Fusion	KIAA1549-BRAF.K13B9	3
BRAF	KIAA1549-BRAF.K14B11.COSF1226	Fusion	KIAA1549-BRAF.K14B11.COSF1226	3
BRAF	KIAA1549-BRAF.K14B9.COSF483	Fusion	KIAA1549-BRAF.K14B9.COSF483	3
BRAF	KIAA1549-BRAF.K15B10.COSF1283.1	Fusion	KIAA1549-BRAF.K15B10.COSF1283.1	3
BRAF	KIAA1549-BRAF.K15B11.COSF485.1	Fusion	KIAA1549-BRAF.K15B11.COSF485.1	3
BRAF	KIAA1549-BRAF.K15B9.COSF481.1	Fusion	KIAA1549-BRAF.K15B9.COSF481.1	3
BRAF	KIAA1549-BRAF.K16B10	Fusion	KIAA1549-BRAF.K16B10	3
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	KIAA1549-BRAF.K17B10.COSF509	3
BRAF	KIAA1549-BRAF.K18B9.COSF511	Fusion	KIAA1549-BRAF.K18B9.COSF511	3
BRAF	KIAA1549-BRAF.K9B9	Fusion	KIAA1549-BRAF.K9B9	3
BRAF	KLHL7-BRAF.K5B9	Fusion	KLHL7-BRAF.K5B9	3
BRAF	LSM12-BRAF.L3B9	Fusion	LSM12-BRAF.L3B9	3
BRAF	LSM14A-BRAF.L9B9	Fusion	LSM14A-BRAF.L9B9	3
BRAF	MACF1-BRAF.M60B9	Fusion	MACF1-BRAF.M60B9	3
BRAF	MAD1L1-BRAF.M16B9	Fusion	MAD1L1-BRAF.M16B9	3
BRAF	MAD1L1-BRAF.M17B10	Fusion	MAD1L1-BRAF.M17B10	3
BRAF	MKRN1-BRAF.M4B11.COSF1444	Fusion	MKRN1-BRAF.M4B11.COSF1444	3
BRAF	MKRN1-BRAF.M4B9	Fusion	MKRN1-BRAF.M4B9	3
BRAF	MYRIP-BRAF.M16B9	Fusion	MYRIP-BRAF.M16B9	3
BRAF	MZT1-BRAF.M2B11	Fusion	MZT1-BRAF.M2B11	3
BRAF	NUB1-BRAF.N3B9	Fusion	NUB1-BRAF.N3B9	3

Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
BRAF	NUDCD3-BRAF.N4B9	Fusion	NUDCD3-BRAF.N4B9	3
BRAF	NUP214-BRAF.N21B10	Fusion	NUP214-BRAF.N21B10	3
BRAF	PAPSS1-BRAF.P5B9.1	Fusion	PAPSS1-BRAF.P5B9.1	3
BRAF	PLIN3-BRAF.P1B9	Fusion	PLIN3-BRAF.P1B9	3
BRAF	RAD18-BRAF.R7B10	Fusion	RAD18-BRAF.R7B10	3
BRAF	RBMS3-BRAF.R11B11	Fusion	RBMS3-BRAF.R11B11	3
BRAF	RNF11-BRAF.R1B11	Fusion	RNF11-BRAF.R1B11	3
BRAF	RNF130-BRAF.R3B9.COSF1483	Fusion	RNF130-BRAF.R3B9.COSF1483	3
BRAF	RP2-BRAF.R3B10	Fusion	RP2-BRAF.R3B10	3
BRAF	SLC12A7-BRAF.S17B11	Fusion	SLC12A7-BRAF.S17B11	3
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	SLC45A3-BRAF.S1B8.COSF871	3
BRAF	SND1-BRAF.S10B11	Fusion	SND1-BRAF.S10B11	3
BRAF	SND1-BRAF.S10B9	Fusion	SND1-BRAF.S10B9	3
BRAF	SND1-BRAF.S11B11	Fusion	SND1-BRAF.S11B11	3
BRAF	SND1-BRAF.S14B11	Fusion	SND1-BRAF.S14B11	3
BRAF	SND1-BRAF.S14B9	Fusion	SND1-BRAF.S14B9	3
BRAF	SND1-BRAF.S16B9.1	Fusion	SND1-BRAF.S16B9.1	3
BRAF	SND1-BRAF.S18B10	Fusion	SND1-BRAF.S18B10	3
BRAF	SND1-BRAF.S9B2	Fusion	SND1-BRAF.S9B2	3
BRAF	SND1-BRAF.S9B9	Fusion	SND1-BRAF.S9B9	3
BRAF	SOX6-BRAF.S5B9	Fusion	SOX6-BRAF.S5B9	3
BRAF	SOX6-BRAF.S6B9	Fusion	SOX6-BRAF.S6B9	3
BRAF	STRN3-BRAF.S3B10	Fusion	STRN3-BRAF.S3B10	3
BRAF	TANK-BRAF.T4B9	Fusion	TANK-BRAF.T4B9	3
BRAF	TAX1BP1-BRAF.T8B11.1	Fusion	TAX1BP1-BRAF.T8B11.1	3
BRAF	TMEM178B-BRAF.T2B9	Fusion	TMEM178B-BRAF.T2B9	3
BRAF	TMPRSS2-BRAF.T3B11	Fusion	TMPRSS2-BRAF.T3B11	3
BRAF	TRIM24-BRAF.T10B9	Fusion	TRIM24-BRAF.T10B9	3
BRAF	TRIM24-BRAF.T11B2	Fusion	TRIM24-BRAF.T11B2	3
BRAF	TRIM24-BRAF.T3B10	Fusion	TRIM24-BRAF.T3B10	3
BRAF	TRIM24-BRAF.T3B11	Fusion	TRIM24-BRAF.T3B11	3
BRAF	TRIM24-BRAF.T5B8	Fusion	TRIM24-BRAF.T5B8	3
BRAF	TRIM24-BRAF.T9B9.1	Fusion	TRIM24-BRAF.T9B9.1	3
BRAF	TRIM4-BRAF.T6B10	Fusion	TRIM4-BRAF.T6B10	3
BRAF	UBN2-BRAF.U3B11	Fusion	UBN2-BRAF.U3B11	3
BRAF	ZC3HAV1-BRAF.Z3B10	Fusion	ZC3HAV1-BRAF.Z3B10	3

Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
BRAF	ZC3HAV1-BRAF.Z7B11	Fusion	ZC3HAV1-BRAF.Z7B11	3
BRAF	ZKSCAN5-BRAF.Z2B9	Fusion	ZKSCAN5-BRAF.Z2B9	3
BRAF	ZSCAN30-BRAF.Z3B10	Fusion	ZSCAN30-BRAF.Z3B10	3
BRAF	COSM1125	SNV	L597Q	3
BRAF	COSM1126	SNV	L597S	3
BRAF	COSM21612	SNV	F595L	3
BRAF	COSM449	SNV	G464E	3
BRAF	COSM451	SNV	G466V	3
BRAF	COSM450	SNV	G464V	3
BRAF	COSM459	SNV	G469V	3
BRAF	COSM460	SNV	G469A	3
BRAF	COSM461	SNV	G469E	3
BRAF	COSM462	SNV	N581S	3
BRAF	COSM466	SNV	D594V	3
BRAF	COSM467	SNV	D594G	3
BRAF	COSM470	SNV	L597V	3
BRAF	COSM471	SNV	L597R	3
BRAF	COSM472	SNV	T599I	3
BRAF	COSM478	SNV	K601E	3
PIK3CA	COSM754	SNV	p.N345K	2
PIK3CA	COSM757	SNV	p.C420R	3
PIK3CA	COSM759	SNV	p.P539R	3
PIK3CA	COSM760	SNV	p.E542K	3
PIK3CA	COSM763	SNV	p.E545K	3
PIK3CA	COSM764	SNV	p.E545G	3
PIK3CA	COSM765	SNV	p.E545D	2
PIK3CA	COSM767	SNV	p.Q546P	3
PIK3CA	COSM775	SNV	p.H1047R	2
PIK3CA	COSM776	SNV	p.H1047L	3
PIK3CA	PIK3CA	CNV	PIK3CA amplification	3
PIK3CA	COSM12458	SNV	p.E545A	3
PIK3CA	COSM766	SNV	p.Q546K	3
PIK3CA	COSM12590	SNV	p.T1025S	3
PIK3CA	COSM12591	SNV	p.M1043V	3
PIK3CA	COSM29313	SNV	p.M1043I	3
PIK3CA	COSM94984	SNV	p.M1043I	3
PIK3CA	COSM773	SNV	p.M1043I	3

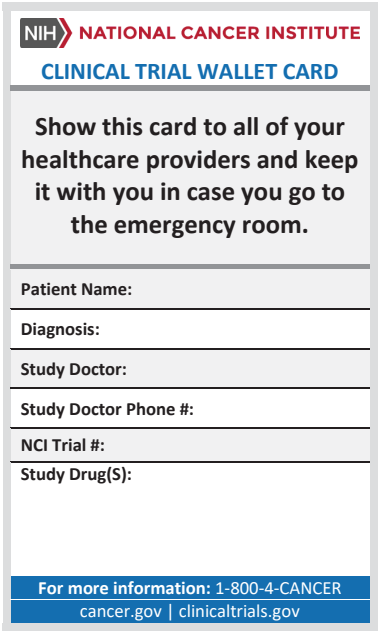
Exclusion Variants				
Gene Name	**Variant ID**	**Variant Type**	**Variant Description**	**Level of Evidence Code**
PIK3CA	COSM774	SNV	p.H1047Y	3
PIK3R1	COSM85926	SNV	p.R348*	3
AKT1	COSM33765	SNV	p.E17K	3
MTOR	COSM1686998	SNV	p.S2215F	3
MTOR	COSM20417	SNV	p.S2215Y	3
MTOR	COSM462604	SNV	p.F1888L	3
MTOR	COSM893813	SNV	p.F1888L	3
MTOR	OM5	SNV	p.F1888L	3
MTOR	OM7	SNV	p.F1888I	3
MTOR	COSM180789	SNV	p.E1799K	3
MTOR	OM9	SNV	p.C1483W	3
MTOR	COSM462616	SNV	p.C1483F	3
MTOR	COSM462615	SNV	p.C1483Y	3
MTOR	OM12	SNV	p.C1483R	3
MTOR	COSM180789	SNV	p.E1799K	3
MTOR	COSM414183	SNV	p.L2209V	3
MTOR	COSM462592	SNV	p.A2210P	3
MTOR	COSM462618	SNV	p.L1460P	3
MTOR	COSM462619	SNV	p.A1459P	3
MTOR	COSM527403	SNV	p.N2206S	3
MTOR	COSM1560108	SNV	p.S2215P	3
MTOR	COSM3965698	SNV	p.L2216P	3
MTOR	MCH4	SNV	p.R2217W	3

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1G: Copanlisib, PTEN Loss

Rev. Add25

Appendix II

Patient Clinical Trial Wallet Card


NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1G: Copanlisib, PTEN Loss

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. • If the repeated glucose value is decreasing, the glucose may be followed without glucose lowering medication treatment if hydration status is normal as clinically assessed. • Consultation with endocrinologist is recommended	• Hydration if appropriate • **When planning next infusion consider prophylaxis with oral glucose lowering medication**
Symptomatic or persisting glucose increases > 250mg/dL	• Hydration status should be clinically assessed. • If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV). • Laboratory test confirming increase should be repeated. If the repeated glucose value is persistent and/or patient is symptomatic and/or the hydration status indicates the need for hydration, glucose lowering medication should be administered. • Prompt input from a diabetes specialist should be obtained.	• Hydration if appropriate • Rapid/ short acting insulin may be given for glucose persisting at > 250 mg/dL, or if the patient is symptomatic during the infusion day. • Rapid/short acting insulin • According to the institution sliding scale coverage of glucose persisting at > 250 mg/dL is recommended, with oral or IV hydration as clinically appropriate • **When planning next infusion consider prophylaxis with oral glucose lowering medication**

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1G: Copanlisib, PTEN Loss

Appendix IV

Dose Modification of Copanlisib for Arterial Hypertension

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