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

November 10, 2022

[redacted] MS RAC
[redacted]
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room [redacted]
Bethesda, MD 20892

Dear Ms. [redacted]

Enclosed is Addendum #31 to EAY131-Z1K, *MATCH Treatment Subprotocol Z1K: Ipatasertib in Patients with Tumors with AKT Mutations.*

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

Re: Review of **Amendment #42** of Protocol **#EAY131-Z1K:** "MATCH Treatment Subprotocol Z1K: Ipatasertib in Patients with Tumors with AKT Mutations"

I. Recommendations:

#	Section	Comments
1.	Appendix V	On page 1 of the patient handout, please remove "BVD-523B (ulixertinib)" and replace with "Ipatasertib." **PI Response:** This change has been made.

The following revisions to the EAY131-Z1K protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	Appendix V	Study drug listed on page 1 of patient handout updated to Ipatasertib.

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The following revisions to the EAY131-Z1K 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 [redacted] or 857-504-2900.

We request review and approval of this addendum to EAY131-Z1K so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

[redacted]

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

EAY131-Z1K

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Z1K: Ipatasertib in Patients with Tumors with AKT Mutations

IPATASERTIB TREATMENT SUBPROTOCOL CHAIR: [redacted] MD, MS
IPATASERTIB TREATMENT SUBPROTOCOL CO-CHAIR: [redacted] MD

Version Date: November 10, 2022

NOTE: This subprotocol (EAY131-Z1K) should be used in conjunction with the MATCH Master Protocol (EAY131).

SUBPROTOCOL ACTIVATION DATE
Incorporated in Addendum #20
Addendum #25
Addendum #30
Addendum #31

Agent	IND#	NSC#	Supply
Ipatasertib (GDC-0068)	ND Sponsor: DCTD, NCI IND#: [redacted]	781451	NCI Supplied

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Rev. Add25
Rev. Add30

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Schema

Cycle = 28 days
Accrual Goal: 35

1. Introduction

1.1 Ipatasertib

Ipatasertib (GDC-0068) is a selective, ATP-competitive inhibitor of AKT[21]. *In vitro*, Ipatasertib inhibits all 3 isoforms of AKT (IC_{50} of AKT1, AKT2 and AKT3 of 5, 18 and 8nM respectively).[1] Screening against a broad panel of 225 kinases determined that Ipatasertib is highly selective, acting as a potent inhibitor against only three additional kinases (including > 70% inhibition against p70S6K – IC_{50} is 860 nM). Thus, Ipatasertib displays a > 100-fold selectivity for AKT1 over the next most potentially inhibited non-AKT kinase, i.e. p70S6K. In PC-3 (PTEN mutant, prostate), BT474M1 (PIK3CA mutant, HER2+ breast), and IGROV-1 (PTEN and PIK3CA mutant, ovarian) cell lines, downstream targets of AKT including PRAS40, Fox01, Fox03, 4EBP1, and S6 are inhibited in a dose- and time-dependent manner.[22] In PC-3, BT474M1 and MCF7-neo/HER2 (PIK3CA mutant, HER2+ breast) cells, a dose-dependent increase in G_0-G_1 phase population has been identified, as well as an increase in apoptotic and necrotic populations in the breast cell lines, as determined by Annexin V/PI staining. Sensitivity to Ipatasertib is strongly associated with pAKT levels above the median value, as well as with loss of PTEN/PTEN mutation. Cell lines with a PIK3CA kinase mutation (i.e. exon 20) also demonstrate increased sensitivity, while those with a helical (i.e. exon 9) or other domain mutation do not. Genentech/Roche has internal data that confirm the growth factor-independent activation of AKT by AKT1 mutations E17K, L52R, D323H, D323Y, Q79K, W80R, AKT2 mutation E17K, and AKT3 mutation E17K. All of these mutations sensitize cells to Ipatasertib in an IL-3-independent BaF3 cell assay. In addition, Ipatasertib demonstrated robust tumor growth inhibition in xenograft models of human cancer cell lines with alterations known to lead to AKT activation, such as LNCaP (PTEN-null, prostate), PC3 (PTEN-null, prostate), HGC-27 (PTEN-null, gastric), HCC1954 (PIK3CA mutant, HER2+ breast), TOV-21G (PTEN-null & PIK3CA mutant, ovarian), and 537MEL (PTEN-null, melanoma), as well as PDX models with PTEN loss or PIK3CA mutations.[2]

There are currently no FDA approved AKT inhibitors for cancer treatment. Ipatasertib is currently under investigation in phase I, II, and III clinical trials in castration resistant prostate cancer and metastatic breast cancer (www.clinicaltrials.gov). In a three-stage study[1], 30 patients were enrolled in the dose-escalation (stage I) and 22 patients in the two dose expansion cohorts (11 metastatic breast cancer and 5 patients with metastatic castration-resistant prostate cancer; stage II)), or all solid tumors (n=6, stage III). The most common cancers were breast cancer (n=16) or colorectal cancer (n=14), with a median of 6 prior lines of therapy (range, 1-17). Oral Ipatasertib was administered daily for 21 days followed by 7 days off (21/7 day dosing schedule) every 28 days with doses ranging from 25-800 mg. Dose limiting toxicities (DLTs) at 800 mg were asthenia and nausea. The maximum tolerated dose for Ipatasertib was 600 mg daily on a 21-day on/7-day off schedule which was used for the expansion cohorts in stage II and stage III; however, the recommended dose for further development is 400 mg daily based upon overall tolerability profile. This dose level is being evaluated in continuous daily dosing, as well as 21-day on/7-day off schedule in phase III studies, with the schedule depending on the combination therapy studied.

In 51 treated patients in the single agent study, the most common causally-related grade 2 or greater adverse events across all dose levels were as follows: diarrhea (35%), nausea (27%), asthenia (25%), hyperglycemia (10%), decreased appetite 6%, rash (6%), and vomiting (6%). Grade 3 events were diarrhea (n=4), asthenia (n=3), hypercholesterolemia (n-1), hyperglycemia (n=1), hypophosphatemia (n=1), nausea (n=1), and toxic skin eruption (n=1). No grade 4 events were observed. Timing to the first onset of diarrhea, nausea, fatigue, and rash typically occurred during cycle 1. As proof of mechanism, reduction in the substrates pGSK3β and pPRAS40 was demonstrated in platelet-rich plasma. In terms of exposure, Ipatasertib ≥ 400 mg was associated with pGSK3β reduction ≥ 80%, and even at doses < 100 mg greater than 50% inhibition was observed. In addition, comparing pretreatment and on-treatment tumor biopsies, there was a reduction in pRAS40, pEBP1, pS6, and pmTOR in a dose-dependent manner, as measured by reverse phase protein array.

There is clinical evidence of anti-cancer activity with Ipatasertib. Across all dosing cohorts, 16 of 47 patients (34%) had stable disease or incomplete response, per RECIST criteria, and 6 patients had a progression free survival > 6 months (18% in those who received 400 mg or 600 mg). Of the 41 patients with known molecular status, stable disease was observed in 6/9 patients with PTEN loss, PIK3CA, or AKT mutations in their tumor, as compared to 3/9 who had progression. Those with a PIK3CA mutation (n=6) or AKT mutation (n=1) remained on study longer with Ipatasertib compared to those without these mutations (n=33); median treatment time was 84 vs. 63 days.

Notably, the one patient with an AKT1 mutation (E17K) had a HER2- negative metastatic breast cancer that had progressed on liposomal doxorubicin, cyclophosphamide, and most recently capecitabine (on drug for ~ 90 days); while on Ipatasertib her CA15-3 declined by > 50% and she remained on study for 235 days (confidential: Genentech). These data suggest that AKT inhibition with Ipatasertib may provide a novel therapeutic approach and serve as the rationale for investigating this agent in patients with AKT mutated tumors. In addition to AKT1 E17K mutations, Genentech has internal data that confirm the enhanced sensitivity of AKT1 E17K, L52R and D323H to Ipatasertib. These mutations in AKT isoforms disrupt the PH-Kinase domain interaction resulting in activation of the kinase activity and promote AKT-dependent survival in IL-3-deprived Ba/F3 cells. Additional AKT mutations expected to be sensitive to Ipatasertib include AKT1 Q79K, AKT1 W80R, AKT1 D323Y, AKT1 D323G, AKT2 E17K and AKT3 E17K. If there is additional pre-clinical or clinical data that demonstrates the benefit of AKT inhibition with other AKT1 mutations or mutations in the other AKT isoforms, further discussion about adding these mutations to the panel will occur.

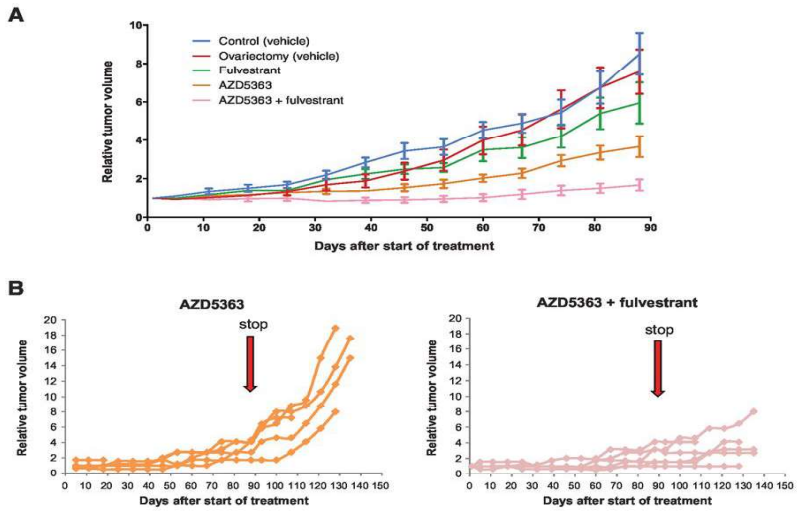

Fig 1: The combination of fulvestrant with AKT inhibition (AZD5363) is better than monotherapy in a hormone refractory model (A). Long-term study changes in tumor volume after withdrawal of AKT inhibitor (B) or the combination (C).

At the 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, a heavily pre-treated patient (10 prior lines) with an AKT1 E17K and ESR D538G mutant ER+ breast cancer was presented[4]. She had previously progressed on fulvestrant as well as AKT inhibition (AZD5363 monotherapy). When fulvestrant was added to the AKT inhibitor on day 121 of AKT inhibitor treatment, follow-up scans showed shrinkage of her primary breast tumor and resolution of liver metastasis. In accordance with these findings, in a phase Ib/II clinical trial in patients with metastatic castration resistant prostate cancer, there was an improved progression free survival advantage in patients who received Ipatasertib 400 mg in combination with abiraterone/prednisone compared to abiraterone/prednisone alone (Investigator's Brochure). These results led to an ongoing phase III trial, evaluating the potential benefit of the combination. These studies demonstrate that the combination of AKT inhibition with hormone therapy may delay or overcome resistance to single-agent hormone therapy treatment in breast and prostate cancer.

1.2 Supporting Preliminary Data

The PI3K-AKT pathway is one of the most commonly altered pathways in cancer, including mutations, somatic copy number abnormalities, increased expression, and aberrant signaling[5,6]. A number of intrinsic and extrinsic survival signals induced by several receptors are thought to be transduced downstream through the PI3K/AKT pathway. In addition, hyperactivity of this pathway promotes resistance to pro-apoptotic signaling induced by chemotherapy and other anti-neoplastic therapies.

Overview of PI3K-AKT pathway:

The PI3K-AKT pathway can be activated upstream by a wide variety of receptor protein tyrosine kinases (RTKs; in particular growth factor receptors), cytokine receptors, intracellular tyrosine kinases, G-protein coupled receptors, and intracellular small GTPases such as Ras[6]. In the case of RTKs, activation by ligand binding results in the non-covalent association of phosphatidylinositol-3 kinases (PI3Ks) with phosphotyrosine consensus motifs on the intracellular domain of the RTK[7]. One or two src-homology 2 (SH2) domains on the beta

(regulatory) subunit of PI3K participate in this interaction, which results in allosteric changes to the catalytic alpha subunit of PI3K, leading to functional activation. The phosphatidylinositol 3,4,5-trisphosphate (PIP3) is generated as a result of phosphorylation by activated PI3K, and resides on the inner side of the plasma membrane. PIP3 is then able to activate a number of proteins, including PDK1, AKT, and other serine/threonine kinases. The pleckstrin homology domain of AKT interacts with PIP3, resulting in transient localization of AKT to the inner membrane and subsequent phosphorylation of the Thr308 and Ser473 residues by phosphoinositide-dependent kinases 1 and 2 (PDK1, PDK2), respectively. PDK1 itself is activated by PIP3, while PDK2 has been recently identified as mTORC2 (the complex rictor/mTOR)[8]. Phosphorylated AKT (p-AKT) represents the active form. The tumor suppressor phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is an important negative regulator of the PI3K/AKT pathway, as it functions to rapidly convert PIP3 back to PIP2[9].

Activation of AKT regulates multiple cellular processes including cell survival, cell proliferation, cell growth, and various aspects of cellular metabolism. AKT (Protein Kinase B) is an evolutionarily conserved serine threonine kinase with 3 forms in mammalian species, AKT1, AKT2, and AKT3, all encoded by different genes[9]. AKT represents an important signaling hub with well over 100 downstream target proteins that it is able to activate or inactivate through phosphorylation of serine and threonine residues. AKT modulates cell survival, cell cycle progression, and cellular growth through phosphorylation of these downstream targets, including inhibition of Bad and caspase 9, phosphorylation of Mdm2 leading to p53 ubiquitination, and phosphorylation of mTOR, respectively[10]. Although the subset of downstream AKT effectors that are most crucial for tumor development have not been entirely elucidated, there is substantial evidence that mammalian target of rapamycin complex 1 (mTORC1) plays an important role. AKT activates mTORC1 by several mechanisms including phosphorylation and inhibition of the tumor suppressor tuberous sclerosis complex 2 (TSC2) that binds to and negatively regulates mTORC1 activity (Fig 2)[11].

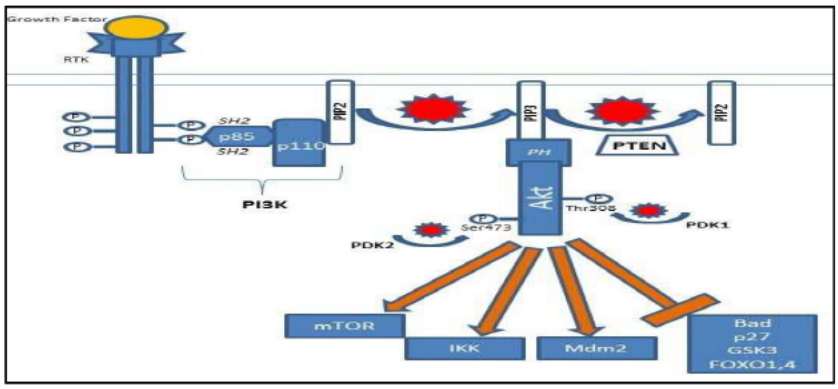

Fig 2: The PI3K/AKT pathway. The role of AKT and downstream effectors are demonstrated.

Alterations to the PI3K-AKT pathway in cancer:

Mutations in genes encoding for the subunits of PI3K represent some of the most commonly mutated genes in all of cancer, with kinase domain activating point mutations in the PIK3CA gene (which encodes for p110α), second only to p53 as the most commonly occurring mutations in all tumor specimens in The Cancer

Genome Atlas (TCGA)[12]. PTEN loss of function mutations, silencing by methylation and other epigenetic changes, and large scale chromosomal changes leading to loss of PTEN are also amongst the more common aberrations seen across many different cancer types, and in particular in metastatic cancer. Germline mutations in PTEN are responsible for the Cowden familial cancer syndrome. Mutations in PTEN and PIK3CA do not appear to be mutually exclusive, underscoring the complex functioning of the various components of the PI3K-AKT pathway[13].

On the other hand, mutations in AKT genes are rarely found in human cancers to date[13]. Activating mutations have been described in a small percentage of breast cancers, head and neck squamous cell carcinomas, endometrial cancer, non-small cell lung cancer, and renal cancers[14]. An AKT1 point mutation in the pleckstrin homology domain that replaces a glutamic acid with lysine (E17K) at residue 17 is the most commonly reported mutation, and is thought to confer increased activity by promoting its localization to the plasma membrane[14]. AKT E17K mutation, for example, is seen in 2-3% of breast cancer, and other AKT mutations have been seen in this tumor as well (BROAD, SANGER, TCGA). AKT1 mutations were seen in luminal A, B and the HER2 subset, but not in basal type. Other activating mutations reported in the literature include the E49K (AKT1) and G171R substitutions (AKT3), which occur in the pleckstrin homology domain and in the kinase domain, respectively. Measurement of p-AKT levels in both tumors and cancer cell lines confirms a quantitative increase in activated AKT as a consequence of these point mutations, and overall levels of p-AKT appear to correlate with sensitivity to AKT inhibition[14].

In addition to mutations, there are other means of augmenting AKT activity, including AKT gene amplification and AKT rearrangements. However, there is no evidence of pre-clinical or clinical benefit of an AKT inhibitor, such as Ipatasertib, with AKT amplifications or fusions[16-18]. To date there is no approved targeted treatment for patients with AKT mutations; this trial may produce clinical validation data that such patients can respond to an AKT inhibitor.

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1.3 Exclusion of Breast Cancer

Due to recent findings that an excess of breast cancer patients (n=18/26) have been accrued to the trial it is now necessary to limit their accrual to avoid overrepresentation of tumors of a particular subtype that would make the ‘tumor agnostic’ intent of the subprotocol unachievable. This has been modified under ‘eligibility criteria.’

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 an AKT mutation as determined via the MATCH Master Protocol and described in Appendix II. See Appendix II for information on the AKT mutation and corresponding Levels of Evidence.

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_____ 2.1.3 Patients with breast cancer are excluded.

_____ 2.1.4 Patients with castration-resistant prostate cancer should maintain castrate levels of testosterone (i.e., with GnRH agonists or through surgical castration). Patients are allowed to continue abiraterone acetate / prednisone with Ipatasertib if the patient just progressed on abirterone acetate / prednisone.

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

_____ 2.1.6 Patients with known KRAS, NRAS, HRAS, or BRAF mutations are not eligible for this protocol, as these mutations may lead to limited response due to resistance.

_____ 2.1.7 Patients with diabetes or risk for hyperglycemia are eligible. Patients with diabetes mellitus should be on a stable dose of oral hypoglycemic agents for ≥ 4 weeks and appropriate diet. Patients with diabetes mellitus may enter the study unless any of the following exclusion criteria are fulfilled:

- Baseline fasting glucose value of >8.9 mmol/L or 160 mg/dL (fasting is defined as no calorific intake for at least 8 hours)
- Patients not on a stable dose of oral hypoglycemic medication for ≥ 4 weeks and appropriate diet
- Insulin required for routine diabetic management and control
- More than two oral hypoglycemic medications required for routine diabetic management and control
- Hemoglobin A1C ≥ 7.5%

_____ 2.1.8 Prior PI3K and mTOR inhibitors are allowed, including in the metastatic setting. Prior AKT inhibitors are excluded (See Appendix IV).

_____ 2.1.9 Patients with a history of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) or active diverticulitis are not eligible.

_____ 2.1.10 Patients may not have received strong inhibitors or potent inducers or substrates of CYP3A4/5 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort). See Section 5.1.8 and Appendix III.

_____ 2.1.11 In addition to the patient contraception requirements outlined in EAY131 MATCH Master Protocol, male patients must also refrain from donating sperm for the duration of study participation, and for 4 months after completion of study.

_____ _____

Physician Signature Date

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

3. Ipatasertib Treatment Plan

3.1 Administration Schedule

Patients will be instructed to take Ipatasertib 400 mg orally once daily continuously for each 28 day cycle, until tumor progression or unless patient experiences unacceptable toxicities. Cycles are defined in 28-day periods to facilitate scheduling of visits and assessments.

NOTE: Ipatasertib can be taken with or without food.

If a dose is missed or omitted (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose the following day. Missed, omitted, or vomited doses will not be made up. In the event that a patient vomits later than 30 minutes after Ipatasertib dosing, the patient must not retake new capsule(s)/tablet(s), but continue to take the next day. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 8 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the Ipatasertib capsule(s) / tablets(s) on time.

Rev. Add25

Hormone Therapy (Breast Cancer and/or Prostate Cancer)

If the patient has HR positive/HER2 negative unresectable breast cancer, (s)he is allowed to continue fulvestrant or an aromatase inhibitor (anastrazole, letrozole, exemestane) with Ipatasertib if (s)he most recently progressed on this anti-estrogen therapy. For instance, if the last treatment was fulvestrant, the patient is allowed to continue the fulvestrant in combination with Ipatasertib. If the patient previously was receiving GnRH agonist (such as leuprolide or goserelin), this should continue as previously administered.

SERMs, such as tamoxifen or toremifene, are not allowed.

If the patient has metastatic castration resistant prostate cancer, he is allowed to continue abiraterone if he just progressed on this agent. GnRH agonists (such as leuprolide or goserelin) are allowed. Prednisone/prednisolone is allowed along with this combination – up to 10 mg po daily (5 mg po bid is allowed).

The patient should continue on the same dose and schedule of the prior hormone therapy as was previously taken. Hormone therapy administration is per FDA-approved package labeling.

Diarrhea Prophylaxis

In this study all patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

3.2 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.

3.2.1 Additional instructions, requirements and exceptions for protocol EAY131 – Subprotocol Z1K

Additional Instructions

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

EAY131 – Subprotocol Z1K 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 Ipatasertib, or within 28 days of the female patient's last dose of Ipatasertib, 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 Z1K specific expedited reporting exceptions:

For Subprotocol Z1K, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

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

3.2.2 Second Primary Cancer Reporting Requirements

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

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.

2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Complete a Second Primary Form in Medidata Rave within 14 days
2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

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

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

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

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

3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipatasertib (NSC 781451)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 188 patients.* Below is the CAEPR for Ipatasertib.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.0, September 16, 2021[1]

Adverse Events with Possible Relationship to Ipatasertib (CTCAE 5.0 Term) [n= 188]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
Diarrhea		Colitis	***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea		Mucositis oral	***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatotoxicity)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
INVESTIGATIONS			
		Neutrophil count decreased	
		Platelet count decreased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***

Adverse Events with Possible Relationship to Ipatasertib (CTCAE 5.0 Term) [n= 188]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Hyperglycemia		*Hyperglycemia (Gr 2)*
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		*Dysgeusia (Gr 2)*
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Rash[2]		*Rash[2] (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]Rash may include rash with or without pruritus, toxic skin eruption, and rash maculo-papular.

Adverse events reported on Ipatasertib trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipatasertib caused the adverse event:

CARDIAC DISORDERS - Cardiac arrest

GASTROINTESTINAL DISORDERS - Abdominal distension; Gastroesophageal reflux disease

INFECTIONS AND INFESTATIONS - Skin infection

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Cholesterol high; Investigations - Other (blood insulin increased); Investigations - Other (glucose urine present)

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypertriglyceridemia; Hyperlipidemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Myalgia

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Paresthesia

RENAL AND URINARY DISORDERS - Acute kidney injury; Glucosuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Skin and subcutaneous tissue disorders - Other (toxic skin eruption)

VASCULAR DISORDERS - Hypotension; Thromboembolic event

NOTE: Ipatasertib 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.

3.4 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)

Patients will be monitored closely for toxicity and the dose of Ipatasertib may be adjusted as indicated in Table 1. Intra-patient dose reduction will be allowed depending on the type and severity of toxicity encountered.

If dose reduction is required, reduction is permanent and will not be brought back up to full dose. If doses are missed due to toxicity, these will not be made up.

Table 1: Dose Levels for Ipatasertib

Dose Level	Daily Dose/ Route	Dispensed As	Schedule
Starting dose level: 0	400 mg, PO	2 × 200-mg tablets	Once daily continuously for each 28 day cycle
–1	300 mg, PO	1 x 200 mg tablet 1 x 100 mg tablet	Once daily continuously for each 28 day cycle
–2	200 mg, PO	1 x 200-mg tablet	Once daily continuously for each 28 day cycle

Patients requiring more than 2 dose reductions due to treatment-toxicity will be removed from treatment. Patients requiring treatment to be held for >4 weeks will be taken off treatment.

Table 2: Hematologic Toxicity

Grade	Management/Next Dose for Ipatasertib
Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3	Hold* until ≤ Grade 2. Consider resuming at one dose level lower, per investigator discretion**.
Grade 4	Hold* until ≤ Grade 2. Resume at one dose level lower**.

* Patients requiring Ipatasertib delay of >4 weeks will go off protocol therapy. Growth factor support is allowed, per investigator discretion. Transfuse PRBC as clinically indicated

** Patients requiring > 2 dose reductions of Ipatasertib will go off protocol therapy.

Table 3: Non-Hematologic Toxicities (except for diarrhea, nausea/vomiting, hyperglycemia. rash, pneumonitis, or hepatotoxicity)

Grade	Management/Next Dose for Ipatasertib
Grade 1	No change in dose
Grade 2	Hold* until ≤ Grade 1. Recommend resume at same dose level, but per investigator discretion. If the toxicity is deemed probably or definitely related to Ipatasertib – and not reduced after the first occurrence - a dose reduction should be considered after a second recurrence, if still deemed probably or definitely related.
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower**.
Grade 4	Hold* until ≤ Grade 1. Resume at one dose level lower or discontinue, per investigator discretion**.
* Patients requiring a delay of >4 weeks will be removed from protocol therapy. ** Patients requiring > two dose reductions will be removed from protocol therapy.	

Table 4: Diarrhea Management

Diarrhea Prophylaxis

In this study all patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

Grade	Management/Next Dose for Ipatasertib
Grade 1	• No change in dose. • Manage with loperamide 4 mg initially, and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea-free interval (maximum daily total dose should not exceed 16 mg). • Dietary modifications such as avoiding any lactose-containing foods. • Hydration with 8–10 glasses of clear liquid such as broth and low-sugar electrolyte infused drinks per day.
Grade 2	• Interrupt Ipatasertib until diarrhea improves to Grade ≤ 1. • Ipatasertib can be resumed at the same dose or one dose lower per investigator evaluation upon improvement to Grade ≤ 1. • Manage with loperamide 4 mg initially, and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea-free interval (maximum daily total dose should not exceed 16 mg). • Dietary modifications such as avoiding any lactose-containing foods. • Hydration with 8–10 glasses of clear liquid such as broth and low-sugar electrolyte infused drinks per day. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines.

Grade	Management/Next Dose for Ipatasertib
	• Reduce Ipatasertib by one additional dose level for recurrent Grade 2 diarrhea.
Grade 3	• Treatment per Grade 2 management guidelines and supportive care. • Interrupt Ipatasertib until diarrhea improves to Grade ≤ 1. • Ipatasertib should be reduced by one dose level when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce Ipatasertib by one additional dose level or permanently discontinue Ipatasertib, per investigator discretion.
Grade 4	• Management as per Grade 3 guidelines. • Permanently discontinue Ipatasertib.
* Patients requiring a delay of > 4 weeks will go off protocol therapy. ** Patients requiring > two dose reductions will go off protocol therapy.	

Table 5: Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron (or equivalent anti-emetic).

Grade	Management/Next Dose for Ipatasertib
Grade 1	• Provide maximum supportive care as needed.
Grade 2	• Provide maximum supportive care as needed. • Provide ondansetron (or equivalent anti-emetic medication) as needed.
Grade 3	• Hold* until ≤ Grade 2. • Provide maximum supportive care as needed. • Provide ondansetron (or equivalent anti-emetic medication) as needed. • If Grade ≥ 3 nausea or vomiting recurs, Ipatasertib should be reduced by one dose level when treatment is restarted.**
Grade 4	• Follow grade 3 recommendations
* Patients requiring a delay of > 4 weeks will go off protocol therapy. ** Patients requiring > two dose reductions will go off protocol therapy.	

Hyperglycemia

These guidelines are for random or fasting blood glucose results. These are general recommendations: due consideration should be given to baseline values and time since food when interpreting glucose results.

It is recommended that approaches to the management of Ipatasertib-induced hyperglycemia in diabetic patients include advice from the patient's endocrinologist where appropriate.

Home glucose measurements may be used to trigger contact between patient and the investigative site team and may lead to an unscheduled clinic visit to

assess glucose. Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance.

For Glucose Level 3 or 4 hyperglycemia, when insulin therapy is considered, an insulin infusion is recommended. Avoid use of long acting insulin, avoid large boluses of short acting insulin, and observe closely for rebound hypoglycemia.

The management recommendations described in Table 6 are based on those detailed by Busaidy et al[21] for PI3K-AKT-mTOR pathway inhibitors.

Table 6: Hyperglycemia

Glucose Level	**Management/Next Dose for Ipatasertib**
Level 1 (<8.9 mM; OR <160 mg/dL)	• No change in dose. • Patient should receive education on a diabetic diet. • Consider home glucose monitoring, as per treating physician discretion.
Level 2 (≥ 8.9 mM and < 13.9 mM; OR > 160 mg/dL and < 250 mg/dL)	• Hold* until ≤ Glucose Level 1. • Initiate home glucose monitoring, as per treating physician discretion. • Add or administer a higher dose of oral metformin. • Consider endocrinology input • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level. Otherwise, no dose reduction required. • If random glucose > 200 mg/dL after 2 weeks of metformin, continue metformin and consider adding sulfonylurea and titrate. • If random glucose > 200 mg/dL after additional 1 week of metformin and sulfonylurea, consider adding basal insulin. Titrate off insulin when medically appropriate.
Level 3 (≥ 13.9 mM and < 27.8mM; OR ≥ 250 mg/dL and < 500 mg/dL) without symptoms, i.e. polyphagia, polydipsia and polyuria.)	• Hold* until ≤ Glucose Level 1. Resume at one dose level lower**. • Immediate endocrinology input and home glucose monitoring, as per treating physician discretion. • Treat hyperglycemia as *medically appropriate*. • Start (or increase) metformin and sulfonylurea and rapidly titrate oral agents. • If random glucose > 200 mg/dL after additional 1 week of metformin and sulfonylurea, consider adding basal insulin. Titrate off insulin when medically appropriate.
Level 4 (≥ 27.8 mM OR ≥ 500 mg/dL) OR (≥ 13.9 mM and < 27.8mM; OR ≥ 250 mg/dL and < 500 mg/dL with symptoms, i.e.	• Hold* until ≤ Glucose Level 1. Resume at one dose level lower or discontinue, per investigator discretion** Immediate endocrinology input. • Treat hyperglycemia as *medically appropriate*. • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin).

Glucose Level	Management/Next Dose for Ipatasertib
polyphagia, polydipsia and polyuria.)	• Consider intravenous fluids and/or admit if hypovolemic signs/symptoms. • Consider appropriate clinical management of hyperglycemia per local guidelines (insulin infusion etc.). • If Glucose Level 4 hyperglycemia recurs, permanently discontinue ipatasertib.
* Patients requiring a delay of > 4 weeks will go off protocol therapy. ** Patients requiring > two dose reductions will go off protocol therapy.	

Rash

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction.

Table 7: Rash

Grade	Management/Next Dose for Ipatasertib
Grade 1	• No change in dose. Initiate dermatological treatment, including topical steroid moderate strength bid and oral anti-histamine, if symptomatic.
Grade 2	• Interrupt Ipatasertib until resolution to Grade ≤ 1 or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids
Grade 3	• Interrupt Ipatasertib until resolution to Grade ≤ 1 or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade ≤ 1 or is no longer clinically significant within 28 days, following completion of the steroid taper, Ipatasertib may be resumed at one dose level below the previous dose • If recovery of the skin toxicity to Grade ≤ 1 does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue Ipatasertib
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. • Consider dermatological consultation and skin biopsy. • Ipatasertib should be permanently discontinued.
* Patients requiring a delay of > 4 weeks will go off protocol therapy. ** Patients requiring > two dose reductions will go off protocol therapy.	

Pneumonitis

Pneumonitis is not known to be causally related to any of the study drugs; however, it has been observed with other drugs treating pathways similar to Ipatasertib. Every effort should be made to determine the etiology of dyspnea

and changes in pulmonary function.

Table 8: Pneumonitis

Grade	Management/Next Dose for Ipatasertib
Grade 1	• Continue study drugs. • Perform CT scan and pulmonary function tests. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• Prescribe corticosteroids if there are clinical symptoms and infectious etiology is ruled out. Interrupt Ipatasertib as long as corticosteroids are being given. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • If pneumonitis resolves to Grade ≤ 1 after completion of the steroid taper, Ipatasertib may be resumed at either the previous dose or one dose level below the previous dose per investigator assessment. • For recurrent Grade 2 pneumonitis, Ipatasertib must be resumed at one dose level below the previous dose. • Discontinue Ipatasertib if recovery to Grade ≤ 1 is not evident within 28 days.
Grade 3	• If infectious etiology is ruled out, prescribe corticosteroids as clinically indicated. • Interrupt Ipatasertib as long as corticosteroids are being given. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • If pneumonitis resolves to Grade ≤ 1, following completion of the steroid taper, continue Ipatasertib at one dose level below the previous dose • Discontinue Ipatasertib if recovery to Grade ≤ 1 is not evident within 28 days. • For recurrent non-infectious Grade 3 pneumonitis events, Ipatasertib should be permanently discontinued
Grade 4	• If infectious etiology is ruled out, prescribe corticosteroids as clinically indicated. • Permanently discontinue Ipatasertib. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.
* Patients requiring a delay of > 4 weeks will go off protocol therapy. ** Patients requiring > two dose reductions will go off protocol therapy.	

CT= computed tomography; PFT = pulmonary function test.

Hepatotoxicity

Permanently discontinue Ipatasertib for any patients who develop a **concurrent** grade 2 or greater elevation of ALT and/or AST **along with a** grade 2 or greater elevation of total bilirubin and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria.

Table 9: Hepatotoxicity

Grade	Management/Next Dose for Ipatasertib
Grade 1	• Continue study drug.
Grade 2	• Continue study drug.
Grade 3	• Immediately interrupt Ipatasertib (and abiraterone, if on abiraterone). • On return of LFTs to baseline or to AST and ALT ≤ 3 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart Ipatasertib at previous dose level (and restart abiraterone at reduced dose of 750 mg daily if on abiraterone). • Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. • If another Grade 3 event occurs, interrupt Ipatasertib (and abiraterone, if on abiraterone). On return of LFTs to baseline or to AST and ALT ≤ 3 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart Ipatasertib, reducing the dose by one level (and abiraterone at a reduced dose of 500 mg daily if on abiraterone). • Further Grade 3 occurrences must result in permanent discontinuation of Ipatasertib (and abiraterone, if on abiraterone)
Grade 4	• Permanently discontinue Ipatasertib (and abiraterone, if on abiraterone)
* Patients requiring a delay of > 4 weeks will go off protocol therapy. ** Patients requiring > two dose reductions will go off protocol therapy.	

Hormone Therapy

For those patients with breast cancer or prostate cancer who continue to receive hormone therapy in combination with Ipatasertib, the hormone therapy has a distinct toxicity profile. While there is the possibility that they may share some adverse events such as fatigue or nausea and causality will not always be clear, dose reductions and/or delays will follow the most conservative approach.

Refer to the FDA-approved package labeling for any dose reductions with the hormone therapy.

There will be no dose adjustments for aromatase inhibitor. Switching between aromatase inhibitors are not allowed. For instance, if the patient continues on letrozole and is unable to tolerate letrozole, s(he) is not allowed to switch to exemestane.

If the patient is not able to tolerate the continuation of hormone therapy inhibitor, the hormone therapy should be discontinued. However, the patient may remain on the study and continue to take Ipatasertib.

Dose reduction or discontinuation of the hormone therapy should be captured on the case report form.

3.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study. See tables for recommendations of toxicity.

Based on the potential for phototoxicity, advise patients receiving Ipatasertib to avoid excessive sun exposure and to use adequate sunscreen protection if sun exposure is anticipated. Patients should avoid using sunbeds/tanning booths.

3.6 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

3.7 Duration of Follow-Up

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

4. Study Parameters

4.1 Therapeutic Parameters for Ipatasertib Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients on Ipatasertib 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	C1D15[K] C2D15[K]	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]	X[K]			X
Performance status	X	X[J]	X[K]			X
CBC w/diff, plts[B]	X	X[B,J]	X[K]			X[F]
Serum chemistry[B]	X	X[B, J]	X[K]			X[F]
Radiologic evaluation[C]	X			X[C]		X[F]
β-HCG[D]	X					
Toxicity Assessment[E]		X	X		X	X[F]
Pill Count/Diary[G]		X			X	
ECG	X[H]					
Tumor biopsy and blood sample for MATCH Master Protocol[I]				X	X	
Anti-estrogen therapy[L, M]	X	X[N]				
Diarrhea Prophylaxis		X[O]				

1. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).
2. Serum Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, 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, including total bilirubin, SGOT[AST], SGPT[ALT], and alkaline phosphatase, 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). **The chemistry panel is required to be fasting for the first (including C1D15) and second cycle, and recommended to be fasting, but not required, thereafter.** Hyperglycemia management is described in Section 3.4.

3. 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.
4. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.
5. 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 at C1D15 and before every subsequent cycle.
6. 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. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.
7. The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.
8. Within 8 weeks of treatment assignment.
9. 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:
    1. 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.
    2. Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
    3. 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.
4. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this time point: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, platelets; Serum chemistry; Concomitant Medications.
5. The patient will also return for Day 15 (+/- 5 days) for pre-dose on cycle 1 and cycle 2. Fasting basic metabolic panel (including glucose), and CBC w/diff will be collected. Hyperglycemia management is described in Section 3.4.

Rev. Add25 6. If the patient has Hormone Receptor positive, HER2 negative unresectable breast cancer, the patient is allowed to continue the fulvestrant or aromatase inhibitor that (s)he just progressed on. For the aromatase inhibitor, patients are NOT allowed to switch within class (for instance, letrozole to anastrazole). GnRH agonists are allowed to continue as previously administered. Dosing should be followed, as per the FDA-approved package labeling. SERMS, such as tamoxifen or toremifene, are not allowed. This study is no longer accruing patients with metastatic breast cancer.

7. If the patient has castration resistant prostate cancer, he is allowed to continue the abiraterone that he just progressed on. For guidance, it is recommended to follow the prescribing information for abiraterone.
8. If the patient is given Fulvestrant and/or a GnRH agonist, these should be given on D1 of the cycle (+/- 7 days).
9. All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

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.

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 Ipatasertib

5.1.1 Other Names:

GDC-0068, R05532961

5.1.2 Classification:

Oral AKT inhibitor

5.1.3 Mode of Action:

Ipatasertib is a potent, selective, ATP-competitive small-molecule inhibitor of all three isoforms of AKT. Ipatasertib selectively binds to the active conformation of AKT and inhibits its kinase activity.

5.1.4 Storage and Stability:

Storage: Do not store above 25°C / 77°F

If a storage temperature excursion is identified, promptly return ipatasertib to less than 25°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.

Stability: Stability studies are ongoing.

5.1.5 Dose Specifics:

Dosing is described in Section 3.1. Starting dose is 400 mg PO QD continuously *for each 28 day cycle.*

5.1.6 How Supplied:

Genentech supplies and CTEP, DCTD, NCI distributes ipatasertib as 100 mg or 200 mg oval, film-coated tablets in a 30 count bottle. The 100 mg tablet is greyish yellow and the 200 mg tablet is brownish pink. In addition to the ipatasertib drug substance, each tablet contains microcrystalline cellulose, pregelatinized maize starch, croscarmellose sodium, colloidal silicon dioxide, povidone, magnesium stearate and either Opadry II Yellow film coat (100 mg) or Opadry II Pink film coat (200 mg).

5.1.7 Route of Administration:

Oral. Ipatasertib *can be taken with or without food.*

5.1.8 Incompatibilities:

Ipatasertib is primarily metabolized by CYP3A. Strong inhibitors and inducers of CYP3A may result increased or decreased ipatasertib exposures, respectively. The following drugs should be avoided, or used with caution when administering ipatasertib. If using of one of these drugs is necessary, the risks and benefits should be evaluated prior to its concomitant use with ipatasertib:

- Strong CYP3A inhibitors: such as but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, and/or grapefruit juice or grapefruit supplements

- Strong CYP3A inducers: such as but not limited to rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4 substrates with a narrow therapeutic index: such as but not limited to alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine
- Ipatasertib is a moderate inhibitor of CYP3A4. Sensitive substrates with a narrow therapeutic index should be avoided or administered with caution.

5.1.9 Patient Care Implications

Because the PI3K-Akt-mTOR pathway is involved in glucose metabolism, inhibition of this signaling network and its target mTOR can cause hyperglycemia, which is a toxicity common to the class of PI3K-Akt-mTOR inhibitors.

Agents such as proton pump inhibitors (e.g., omeprazole, pantoprazole) are not expected to affect ipatasertib PK.

5.1.10 Side Effects

See Section 3.3 for side effects.

6. Translational Studies

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

7. References

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Molecular Analysis for Therapy Choice (MATCH)
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Appendix I

Patient Pill Calendar

Storage: Store at Room Temperature

Pill Calendar Directions

22. Take your scheduled dose of each tablet at the same time each day.
23. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
24. All doses of Ipatasertib can be taken with or without food.
25. Ipatasertib is to be taken orally once daily.
26. *If you vomit later than 30 minutes after Ipatasertib dosing, do not retake new tablet(s), but continue to take the next dose 24 hours later.*
27. If you miss a dose, you may take the dose up to a maximum of 8 hours after the scheduled dose time. If greater than 8 hours after the scheduled dose time, the missed dose should not be made up.
28. If you need to take the dose earlier for whatever reason, you can take the dose up to 8 hours earlier than the scheduled dose time.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Patient ID: _____

Cycle: ___ Dose Information: _____

Ipatasertib

DAY	Date			Time tablets taken	Number of tablets taken (100 mg)	Number of tablets taken (200 mg)	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year				
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							

DAY	Date Month	Day	Year	Time tablets taken	Number of tablets taken (100 mg)	Number of tablets taken (200 mg)	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
21							
22							
23							
24							
25							
26							
27							
28							

Patient Signature: _____ Date: _____

Patient Pill Calendar (If HR positive/HER2 negative metastatic breast cancer and continuing an aromatase inhibitor)

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of tablets that you take each day.** Ipatasertib is taken daily. The aromatase Inhibitor is taken daily. If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Patient ID: _____

Cycle: ___ Dose Information: _____

				Ipatasertib			Aromatase Inhibitor Name:	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
DAY	Date Month	Day	Year	Time tablets taken	Number of tablets taken (100 mg)	Number of tablets taken (200 mg)	Time 1 tablet taken	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								

				Ipatasertib			Aromatase Inhibitor Name:	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
DAY	Date Month	Day	Year	Time tablets taken	Number of tablets taken (100 mg)	Number of tablets taken (200 mg)	Time 1 tablet taken	
21								
22								
23								
24								
25								
26								
27								
28								

Patient Signature: _____ Date: _____

Patient Pill Calendar (If castration-resistant prostate cancer and continuing abiraterone)

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of tablets that you take each day.** Ipatasertib is taken daily**.** The abiraterone is taken daily. If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Patient ID: _____

Cycle: ___ Dose Information: _____

				Ipatasertib			Abiraterone Name:		Prednisone	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
DAY	Date Month	Day	Year	Time tablets taken	Number of tablets taken (100 mg)	Number of tablets taken (200 mg)	Time tablets taken	Number of tablets taken	Dose	
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										

				Ipatasertib			Abiraterone Name:		Prednisone	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
DAY	**Date** Month	Day	Year	**Time tablets taken**	**Number of tablets taken (100 mg)**	**Number of tablets taken (200 mg)**	**Time tablets taken**	**Number of tablets taken**	**Dose**	
17										
18										
19										
20										
21										
22										
23										
24										
25										
26										
27										
28										

Patient Signature: _____

Molecular Analysis for Therapy Choice (MATCH)
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Appendix II

Actionable Mutations for Sub-Protocol EAY131- Z1K

List of inclusion variants: A function has been implemented in MATCHBOX to identify any activating mutations in AKT gene with a Level of Evidence of code 3 or higher other than what is listed in the table below. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Gene Name	Variant ID	Variant Type	Variant Description	aMOI	Level of Evidence Code
AKT1	COSM33765	SNV	AKT1 mutation	p.E17K	Level 2
AKT1	COSM159008	SNV	AKT1 mutation	p. Q79K	Level 2
AKT1	COSM93893	SNV	AKT1 mutation	p. L52R	Level 3
AKT2	COSM159009	SNV	AKT2 mutation	p. E17K	Level 3
AKT3	COSM224779	SNV	AKT3 mutation	p. E17K	Level 3

List of exclusion variants:

Gene Name	Variant ID	Variant Description	aMOI
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	BRAF Fusion	AGTRAP-BRAF.A5B8.COSF828.1
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	BRAF Fusion	AKAP9-BRAF.A8B9.COSF1013.1
BRAF	CDC27-BRAF.C16B9.1	BRAF Fusion	CDC27-BRAF.C16B9.1
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	BRAF Fusion	FAM131B-BRAF.F2B9.COSF1189.1
BRAF	FCHSD1-BRAF.F13B9.COSF404.1	BRAF Fusion	FCHSD1-BRAF.F13B9.COSF404.1
BRAF	KIAA1549-BRAF.K15B11	BRAF Fusion	KIAA1549-BRAF.K15B11
BRAF	KIAA1549-BRAF.K15B9	BRAF Fusion	KIAA1549-BRAF.K15B9
BRAF	KIAA1549-BRAF.K16B10.COSF509	BRAF Fusion	KIAA1549-BRAF.K16B10.COSF509
BRAF	KIAA1549-BRAF.K17B10	BRAF Fusion	KIAA1549-BRAF.K17B10
BRAF	KIAA1549-BRAF.K18B9	BRAF Fusion	KIAA1549-BRAF.K18B9
BRAF	PAPSS1-BRAF.P5B9.1	BRAF Fusion	PAPSS1-BRAF.P5B9.1
BRAF	SLC45A3-BRAF.S1B8.COSF871	BRAF Fusion	SLC45A3-BRAF.S1B8.COSF871
BRAF	SND1-BRAF.S16B9.1	BRAF Fusion	SND1-BRAF.S16B9.1
BRAF	TAX1BP1-BRAF.T8B11.1	BRAF Fusion	TAX1BP1-BRAF.T8B11.1

Gene Name	Variant ID	Variant Description	aMOI
BRAF	TRIM24-BRAF.T9B9.1	BRAF Fusion	TRIM24-BRAF.T9B9.1
BRAF	COSM453	BRAF mutation	p.G466E
BRAF	COSM1111	BRAF mutation	p.G464R
BRAF	COSM1125	BRAF mutation	p.L597Q
BRAF	COSM1126	BRAF mutation	p.L597S
BRAF	COSM1127	BRAF mutation	p.V600R
BRAF	COSM1133046	BRAF mutation	p.Y472C
BRAF	COSM1448615	BRAF mutation	p.G464R
BRAF	COSM1583010	BRAF mutation	p.D594A
BRAF	COSM1583011	BRAF mutation	p.V600R
BRAF	COSM211600	BRAF mutation	p.D594N
BRAF	COSM21549	BRAF mutation	p.A598V
BRAF	COSM21612	BRAF mutation	p.F595L
BRAF	COSM253328	BRAF mutation	p.G466R
BRAF	COSM27639	BRAF mutation	p.D594N
BRAF	COSM308550	BRAF mutation	p.V600D
BRAF	COSM447	BRAF mutation	p.R462I
BRAF	COSM448	BRAF mutation	p.I463S
BRAF	COSM449	BRAF mutation	p.G464E
BRAF	COSM450	BRAF mutation	p.G464V
BRAF	COSM451	BRAF mutation	p.G466V
BRAF	COSM452	BRAF mutation	p.G466A
BRAF	COSM459	BRAF mutation	p.G469V
BRAF	COSM460	BRAF mutation	p.G469A
BRAF	COSM461	BRAF mutation	p.G469E
BRAF	COSM462	BRAF mutation	p.N581S
BRAF	COSM463	BRAF mutation	p.E586K
BRAF	COSM466	BRAF mutation	p.D594V
BRAF	COSM467	BRAF mutation	p.D594G
BRAF	COSM468	BRAF mutation	p.F595L
BRAF	COSM469	BRAF mutation	p.G596R
BRAF	COSM470	BRAF mutation	p.L597V
BRAF	COSM471	BRAF mutation	p.L597R
BRAF	COSM472	BRAF mutation	p.T599I

Gene Name	Variant ID	Variant Description	aMOI
BRAF	COSM473	BRAF mutation	p.V600K
BRAF	COSM474	BRAF mutation	p.V600R
BRAF	COSM476	BRAF mutation	p.V600E
BRAF	COSM477	BRAF mutation	p.V600D
BRAF	COSM478	BRAF mutation	p.K601E
BRAF	COSM53198	BRAF mutation	p.F595L
HRAS	COSM480	HRAS mutation	p.G12S
HRAS	COSM481	HRAS mutation	p.G12C
HRAS	COSM482	HRAS mutation	p.G12R
HRAS	COSM483	HRAS mutation	p.G12V
HRAS	COSM484	HRAS mutation	p.G12D
HRAS	COSM485	HRAS mutation	p.G12A
HRAS	COSM486	HRAS mutation	p.G13R
HRAS	COSM487	HRAS mutation	p.G13S
HRAS	COSM488	HRAS mutation	p.G13C
HRAS	COSM489	HRAS mutation	p.G13V
HRAS	COSM490	HRAS mutation	p.G13D
HRAS	COSM496	HRAS mutation	p.Q61K
HRAS	COSM497	HRAS mutation	p.Q61E
HRAS	COSM498	HRAS mutation	p.Q61L
HRAS	COSM499	HRAS mutation	p.Q61R
HRAS	COSM500	HRAS mutation	p.Q61P
HRAS	COSM502	HRAS mutation	p.Q61H
HRAS	COSM503	HRAS mutation	p.Q61H
KRAS	COSM13643	KRAS mutation	p.G12N
KRAS	COSM19404	KRAS mutation	p. A146T
KRAS	COSM30567	KRAS mutation	p.G13E
KRAS	COSM512	KRAS mutation	p.G12F
KRAS	COSM514	KRAS mutation	p.G12L
KRAS	COSM516	KRAS mutation	p.G12C
KRAS	COSM517	KRAS mutation	p.G12S
KRAS	COSM518	KRAS mutation	p.G12R
KRAS	COSM520	KRAS mutation	p.G12V
KRAS	COSM521	KRAS mutation	p.G12D

Gene Name	Variant ID	Variant Description	aMOI
KRAS	COSM522	KRAS mutation	p.G12A
KRAS	COSM527	KRAS mutation	p.G13C
KRAS	COSM528	KRAS mutation	p.G13S
KRAS	COSM529	KRAS mutation	p.G13R
KRAS	COSM532	KRAS mutation	p.G13D
KRAS	COSM533	KRAS mutation	p.G13A
KRAS	COSM534	KRAS mutation	p.G13V
KRAS	COSM538	KRAS mutation	p.G15S
KRAS	COSM539	KRAS mutation	p.G15D
KRAS	COSM549	KRAS mutation	p.Q61K
KRAS	COSM550	KRAS mutation	p.Q61E
KRAS	COSM551	KRAS mutation	p.Q61P
KRAS	COSM552	KRAS mutation	p.Q61R
KRAS	COSM553	KRAS mutation	p.Q61L
KRAS	COSM554	KRAS mutation	p.Q61H
KRAS	COSM555	KRAS mutation	p.Q61H
KRAS	COSM87280	KRAS mutation	p.G13E
NRAS	COSM561	NRAS mutation	p.G12R
NRAS	COSM562	NRAS mutation	p.G12C
NRAS	COSM563	NRAS mutation	p.G12S
NRAS	COSM564	NRAS mutation	p.G12D
NRAS	COSM565	NRAS mutation	p.G12A
NRAS	COSM566	NRAS mutation	p.G12V
NRAS	COSM569	NRAS mutation	p.G13R
NRAS	COSM570	NRAS mutation	p.G13C
NRAS	COSM571	NRAS mutation	p.G13S
NRAS	COSM573	NRAS mutation	p.G13D
NRAS	COSM574	NRAS mutation	p.G13V
NRAS	COSM575	NRAS mutation	p.G13A
NRAS	COSM580	NRAS mutation	p.Q61K
NRAS	COSM581	NRAS mutation	p.Q61E
NRAS	COSM582	NRAS mutation	p.Q61P
NRAS	COSM583	NRAS mutation	p.Q61L
NRAS	COSM584	NRAS mutation	p.Q61R

Gene Name	Variant ID	Variant Description	aMOI
NRAS	COSM585	NRAS mutation	p.Q61H
NRAS	COSM586	NRAS mutation	p.Q61H

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Appendix III

CYP3A4/5 Strong Inducers and Potent Inhibitors

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information. Another reference is the Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers: (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The Principal Investigator should be alerted if the subject is taking any agent on these lists. Appropriate medical judgment is required.

CYP3A4/5 Potent Inhibitors:

Ketoconazole
Protease inhibitors (danoprevir, ritonavir, saquinavir, indanavir, tapranavir, telaprevir, elvitegravir, lopinavir, nelfinavir, bocepravir)
Cobicistat
Conivaptan
Nefazodone
Mebefradil
Itraconazole
Posaconazole
Voriconazole
Clarithromycin
Telithromycin
Troleandomycin

CYP3A4/5 Inducing Agents:

Phenobarbital
Carbamazepine
Phenytoin
Grapefruit or Grapefruit supplements
Rifabutin
Mitotane
Rifampicin
St John's Wort

Molecular Analysis for Therapy Choice (MATCH)
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Appendix IV

PI3K/AKT inhibitors in development

The lists of these agents are constantly changing. This may not be a comprehensive list.

PI3K inhibitors in development:

Drug:	Company	Alt. Names	Targets
BKM-120	Novartis	buparlisib	Pan-p110 isoforms
BYL719	Novartis		p110-α
BEZ235	Novartis		Dual mTOR and pan-p110
CAL-101	Calistoga	idelalisib	p110-δ
IPI-145	Infinity		p110-δ,-γ
GDC-0941	Genentech	Pictilisib	Pan-p110 isoforms
GDC-0980	Genentech	Apitolisib	Dual mTOR and pan-p110
GDC-0032	Genentech		p110-α, -δ,-γ
BAY 80-6946	Bayer	copanlisib	p110-α,-β
PX-866	Oncothyreon		Pan-p110 isoforms
XL147	Exelixis	SAR245408	Pan-p110 isoforms
XL765	Exelixis	SAR245409	Dual mTOR and pan-p110
AMG319	Amgen		p110-δ
PF-05212384	Pfizer	PKI-587	Dual mTOR and p110-α
PF-04691502	Pfizer		Dual mTOR and pan-p110
GSK2126458	GlaxoSmithKline	GSK458	Dual mTOR and pan-p110
BGT-226	Novartis		Dual mTOR and pan-p110
SF1126	Semafore	LY294002	p85 and Pan-p110 isoforms
ZSTK474	Zenyaku Kogyo		Pan-p110 isoforms
GSK2636771	GlaxoSmithKline		p110-β
GSK2269557	GlaxoSmithKline		p110-α
TGR-1202	TG therapeutics	RP5264	p110-δ
MLN1117	Millennium	INK1117	p110-α
CUDC-907	Curis		Dual HDAC (class I and IIB) and p110-α,-β, -δ
P7170	Piramal Enterprises		PI3K/mTOR/ALK-1/DNA-PK
RP-6530	Rhizen		p110-δ,-γ
VS-5584	Verastem	SB2343	Dual mTOR and pan-p110
WX-037	WILEX		Pan-p110 isoforms

AKT inhibitors in development:

Drug:	Company	Alt. Names	Targets
MK-2206	Merck		Pan-AKT isoforms
GSK-690693	GlaxoSmithKline		Pan-AKT isoforms
AZD5363	AstraZeneca		Pan-AKT isoforms
KRX-0401	Keryx	perifosine	Dual AKT and PI3K inhibitor
DNE3			Pan-AKT isoforms
ONC-201	Oncoceutics		Dual AKT and ERK inhibitor
BAY-1125976	Bayer		AKT1,2
GSK-2141795	GlaxoSmithKline	uprosertib	Pan-AKT isoforms
GSK-2110183	GlaxoSmithKline	afuresertib	Pan-AKT isoforms
SR-13668			AKT, 12-LOX
MSC-2363318A	Merck Serono		Dual p70S6K/pan-AKT inhibitor
LY-2780301	Lilly		Dual p70S6K/pan-AKT inhibitor
VD-0002	Vioquest	triciribine	Pan-AKT isoforms
AG1343		nelfinavir; Viracept	HIV protease inhibitor, AKT
miltefosine		Impavido	AKT, PI3K, PKC

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Rev. Add25

Appendix V

PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #:**
Rev. Add31 **t dy Doctor:**	**Study Doctor Phone #:**	**Study Drug(s):** Ipatasertib

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:

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

	Explanation
CYP isoenzymes	The enzyme in question is CYP3A4. Ipatasertib is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme. Ipatasertib is an inhibitor of CYP3A4 and may affect the metabolism of other drugs.

These are the things that you need to know:

The study drug, ipatasertib, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inhibitors or inducers of CYP3A4 or sensitive substrates of CYP3A4."

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

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTI **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI **DRUG INTERACTIONS**	NIH NATIONAL CANCER INSTI
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Ipatasertib interacts with CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme. Ipatasertib is an inhibitor of CYP3A4 and may affect the metabolism of other drugs and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):** Ipatasertib	**Use caution and avoid the following drugs if possible:** Avoid ingestion of grapefruit, grapefruit juice or grapefruit supplements.	Your healthcare providers should be aware of any medicines that are "strong inhibitors or inducers of CYP3A4 or sensitive substrates of CYP3A4." **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. Version JUN/2020	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov

Fold at dotted lines: