July 10, 2019

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

Dear Ms. Kruhm:

Enclosed is Addendum #21 to EAY131-Y, *AZD5363 in Patients with Tumors with AKT Mutations.*

Please replace your current copy of the protocol and Informed Consent document (if ICD changed) with this (these) updated version(s). 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.

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.]

This addendum is in response to Dr. L. Austin Doyle March 29, 2019 Request for Amendment for AZD5363.

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

	Section	Change
1.	Cover Page	Update Version date
2.	3.3	Updated the AZD5363 CAEPR list with version 2.3, February 28, 2019

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

	Section	Change
1.	Page 1	Updated Version Date
2.	What possible risks can I expect from taking part in this study?	Updated the AZD5363 possible risks risk list with version 2.3 February 28, 2019.

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

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

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

Thank you.

Sincerely,

Pamela Cogliano

Protocol Development Manager

Enclosure

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

EAY131-Y

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Y: AZD5363 in Patients with Tumors with AKT Mutations

AZD5363 TREATMENT SUBPROTOCOL CHAIR: Kevin Kalinsky, M.D., M.S.
AZD5363 TREATMENT SUBPROTOCOL CO-CHAIR: Carolyn McCourt, M.D.
AZD5363 TRANSLATIONAL CHAIR: Jasgit Sachdev, M.D.

Version Date: July 10, 2019

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

Rev. Add13 **NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.**

SUBPROTOCOL ACTIVATION DATE

May 31, 2016 (incorporated in Addendum #3)
Addendum #4 – 7/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #11 – 8/17
Addendum #13
Addendum #21

Agent	IND#	NSC#	Supply
AZD5363	IND Sponsor: DCTD, NCI IND#:	782347	NCI Supplied

Table of Contents

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Schema

Cycle = 28 days
Accrual Goal: 35

1. If patient has Hormone Receptor positive, Her2 negative metastatic breast cancer with demonstration of progression on an aromatase inhibitor or fulvestrant, (s)he can continue the aromatase inhibitor or fulvestrant that was just being administered in addition to AZD5363. Patients continuing hormone therapy will start with AZD5363 dosing of 400 mg PO twice a day 4 days on/3 days off on a weekly basis for each 28 day cycle.

1. Introduction

1.1 AZD5363

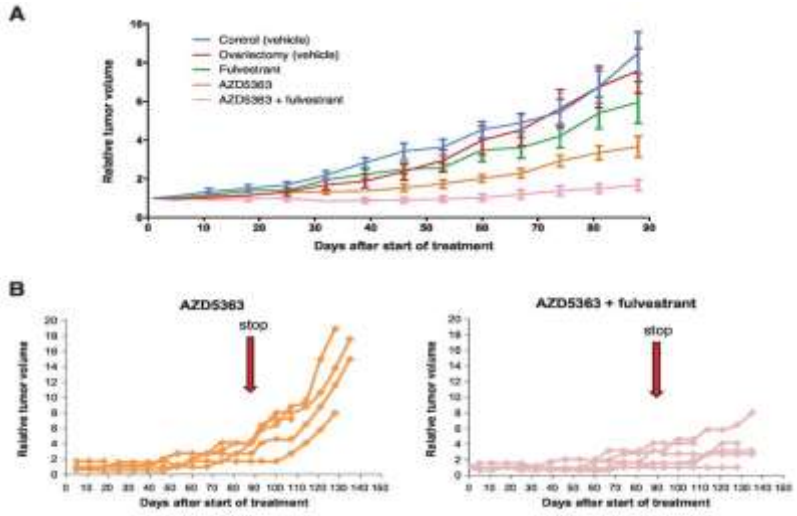
AZD5363 is a potent, pan-AKT inhibitor of the kinase activity of AKT. *In vitro*, AZD5363 inhibits all 3 isoforms of AKT, with an IC_{50} < 10nmol/L AKT ($IC_{50}$of AKT1, AKT2 and AKT3 of 3, 7 and 7nM respectively)[1]. *In vivo*, AZD5363 activity has been demonstrated with inhibition of phosphorylation of the substrates PRAS40, GSK3B, and S6 by 80-90%. The presence of abnormalities in the PI3K/AKT pathway in cell lines, including PIK3CA mutations or PTEN loss or inactivating mutation, correlates with sensitivity to AZD5363[1,2]. Tumor volume decrease has been shown in various xenograft models in immunodeficient mice, including BT474c model (PIK3CA mutant, HER2+ breast cancer), HCC-1952 (PIK3CA mutant, HER2+ breast cancer), 786-0 (PTEN null, VHL null renal cell carcinoma), and HGC27 (PIK3CA mutant, PTEN mutant gastric cancer)[1]. In unpublished data, AZD5363 reverses expression of AKT1 E17K-induced colony formation in mammary epithelial cells (Astra-Zeneca, confidential). In unpublished data, AZD5363 has also demonstrated tumor volume reduction in 2 AKT1 E17K mutant breast cancer explant models [confidential: IB (Investigator's Brochure)]. In human breast cancer (HBC)-x31 explants, mean tumor volume decreased by 89% ($p < 0.001$ compared to controls) (IB, confidential). The tumors in 6 out of 8 mice in the group showed almost complete regression to < 20 mm^3 (IB, confidential). In HBC-x2 explants, AZD5363 inhibited mean tumor volume by 76% compared to controls ($p < 0.001$) (IB, confidential).

There are no FDA approved AKT inhibitors for cancer treatment. AZD5363 is currently under investigation in phase I and II trials (www.clinicaltrials.gov). It is not FDA approved for any indication. At ASCO 2015, data from a phase I trial in patients with PIK3CA mutated breast and gynecologic cancers was presented[3]. In this adaptive design, continuous dosing vs. intermittent dosing (4 days on/3 days off vs. 2 days on/5 days off) was being assessed[3]. In this study, 47, 21 and 22 patients were treated on the continuous dosing [Maximum Tolerated Dose (MTD: 320 mg BID], 4/3 (480 mg BID) and 2/5 schedules (640 mg BID). Dose limiting toxicities (DLTs) were rash and diarrhea for continuous dosing, and hyperglycemia for 2/5. No DLTs were identified for the 4/3 schedule. The most common causally-related grade 3 or greater adverse events were as follows: hyperglycemia (20%), diarrhea (10%), rash (10%), nausea (3%) and fatigue (1%). In accordance, the most common adverse events identified in the IB are diarrhea, hyperglycemia, and hypersensitivity (confidential). As proof of mechanism, reduction in the substrates pGSK3β and pPRAS40 was demonstrated in platelet-rich plasma[3]. Target lesion shrinkage was observed in 7/15 and 4/14 patients in the breast and gynecologic cohorts respectively to date. In PIK3CA mutant breast cancer as a single agent, 2 patients had a partial response (both helical domain PIK3CA mutations, no PTEN loss). There was also 1 patient with gynecological cancer with a partial response (approximately 50% reduction in sum of target diameter), with a mutation in the p85 adaptor binding domain and PTEN null. Patients with PIK3CA mutations are potentailly eligible for protocol I of the NCI Match. Based on the data above, the recommended phase II dose is 480 mg BID, given as 4 days on/3 days off on a weekly basis.

There is clinical evidence of anti-cancer activity with AZD5363 in patients with AKT mutated tumors. At the 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics[4], data were presented on patients with tumors harboring AKT1 mutations who received 480 mg BID, 4 days on/3 days off. Of the 18 patients with estrogen receptor (ER) + metastatic breast cancer, 14 patients demonstrated target lesion shrinkage, with 3 patients having a confirmed partial response and 2 patients with unconfirmed partial responses. Of those with confirmed responses, one patient was on study for 14.3 months prior to progression and one remains on study (3.7 months). In patients with gynecologic tumors, 9 out of 11 patients demonstrated target lesion shrinkage, with 3 patients having confirmed partial responses. One of these patients with endometroid carcinoma of the ovary has been on-study for 39.2 months, with an ongoing partial response. In those with other advanced AKT1 mutant solid tumors, 10 of 12 patients demonstrated target lesion shrinkage, with 1 patient with a metastatic adenocarcinoma of unknown primarily demonstrating a confirmed partial response. These data suggest that AKT inhibition with AZD5363 may provide a novel therapeutic approach and serve as the rationale for investigating this agent in AKT mutated tumors.

In addition, there is recent data that the combination of AZD5363 with endocrine therapy is superior to monotherapy in ER+ breast cancer in endocrine sensitive and endocrine-resistant cell lines[5]. The combination of AZD5363 with endocrine therapy results in a dose-dependent decrease in proliferation in the majority of ER + breast cancer cell lines adapted to LTED (long-term estrogen deprivation) or tamoxifen resistance, including MCF7, HCC1228, T47D, ZR75.1. Thus, the combination leads to a re-sensitization of endocrine-resistant tumors. For instance, AZD5363 re-sensitizes TAM-resistant cells to tamoxifen and acts synergistically with fulvestrant. Treatment with AZD5363 results in a significant reduction of notable PI3K/AKT pathway downstream effectors, such as pPRAS40 and S6 kinase. In a patient-derived luminal breast cancer xenograft HBCx22OvaR with acquired resistance to estrogen deprivation, combination of fulvestrant with AZD5363 causes an almost complete inhibition of tumor grown (80% inhibition). Importantly, the combination is significantly more active than AZD5363 and fulvestrant monotherapy groups (p= 3.75E-03 and 6.3E-04, respectively: Fig 1A). After 90 days of treatment, therapies were withdrawn and tumor volume assessed for efficacy. Removal of AZD5363 leads to a rise in tumor volume within 10 days after withdrawal (Fig 1B). The combination of AZD5363 shows a sustained antitumor effect after 50 days of treatment cessation (Fig 1C).

Fig 1: The combination of fulvestrant with AZD5363 is better than monotherapy in a hormone refractory model (A). Long-term study changes in tumor volume after withdrawal of AZD5363 (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 AZD5363 monotherapy. When fulvestrant was added to AZD5363 on day 121 of AZD5363 treatment, follow-up scans showed shrinkage of her primary breast tumor and resolution of liver metastasis. These studies demonstrate that the combination of AZD5363 with hormone therapy may delay or overcome resistance to AZD5363 monotherapy in hormone receptor positive metastatic breast cancer.

1.2 Supporting Preliminary Data

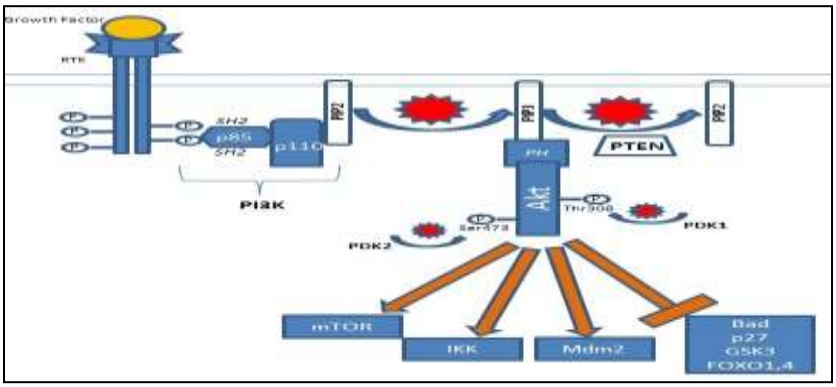
The PI3K-AKT pathway is one of the most commonly altered pathways in cancer, including mutations, somatic copy number abnormalities, increased expression, and aberrant signaling[6]. A number of intrinsic and extrinsic survival signals induced by several receptors are thought to be transduced downstream 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 AZD5363, 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.

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).

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_____ 2.1.2 Patients must have an AKT mutation as determined via the MATCH Master Protocol. See Appendix II for a list of the AKT mutation and corresponding Levels of Evidence.

_____ 2.1.3 Patients with hormone receptor positive, defined as estrogen receptor and/or progesterone receptor > 1% by immunohistochemistry[19], **AND** HER2 negative unresectable breast cancer, with no overexpression by IHC or amplification by in-situ hybridization[20], are allowed to continue fulvestrant or an aromatase inhibitor (anastrazole, letrozole, exemestane) with AZD5363 if patient just progressed on this anti-estrogen therapy. GnRH agonists (such as leuprolide or goserelin) are allowed. For instance, if the last treatment was letrozole plus goserelin, the patient is allowed to continue the letrozole plus goserelin with AZD5363.

NOTE: SERMs, such as tamoxifen or toremifene, are not allowed, given concerns about CYPD26 and CYP3A4 metabolism, respectively.

_____ 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 AZD5363 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 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)
- Insulin required for routine diabetic management and control
- More than two oral hypoglycemic medications required for routine diabetic management and control

_____ 2.1.8 Patients may not have received treatment with another inhibitor of PI3K, AKT or mTOR in the neoadjuvant, adjuvant or metastatic setting with the exception of FDA approved rapalogs. Patients with metastatic cancer, who received PI3K/AKT/mTOR inhibitors on short preoperative window trials (treatment for 4 weeks or less) will be eligible if the treatment was over 6 months prior to registration (See Appendix IV).

_____ 2.1.9 Patients may not have received strong inhibitors or potent inducers or substrates of CYP3A4 or substrates of CYP2D6 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.

_____ _____

Physician Signature Date

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

3. AZD5363 Treatment Plan

Rev. 3/17

3.1 Administration Schedule

Patients will be instructed to take AZD5363 480 mg orally twice daily, 4 days on/3 days off on a weekly basis 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: Twice daily doses should be taken at approximately the same time each morning and evening approximately 12 hours apart.

NOTE: AZD5363 should be taken with water only on an empty stomach, no food for 2 hours prior to dose and for 1 hour after dose.

In the event that a patient vomits after AZD5363 dosing, the patient must not retake new capsule(s)/tablet(s), but continue to take the next dose 12 hours later.

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the AZD5363 capsule(s) / tablets(s) on time.

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 AZD5363 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 AZD5363. SERMs, such as tamoxifen or toremifene, are not allowed.

NOTE: Patients who will be continuing fulvestrant or an aromatase inhibitor will be instructed to take AZD5363 400 mg orally daily twice a day, 4 days on/3 days off on a weekly basis for each 28 day cycle, until tumor progression or unless patient experiences unacceptable toxicities. This is based upon the recommended phase II dosing performed in the phase I trials with AZD5363.

Fulvestrant will be administered 500 mg intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock every 28 days (+/- 7 days). As the patients will have just progressed on fulvestrant, re-loading will not be necessary, and patients can continue on the 28 day schedule. Fulvestrant will be given as standard of care and not supplied by the study.

An aromatase inhibitor (anastrazole 1 mg, letrozole 2.5 mg, or exemestane 25 mg) is allowed to continue, if the patient most recently progressed on this agent. For instance, if s(he) just progressed on anastrozole, anastrazole can continue in combination with AZD5363. If the patient previously was receiving a GnRH agonist (such as leuprolide or goserelin), this should continue as previously administered. Aromatase inhibitors and GnRH agonists will be given as standard of care and not supplied by the study.

If the patient most recently progressed on the combination of fulvestrant plus an aromatase inhibitor, both may agents may continue in combination with AZD5363.

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 Y

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 Y specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on AZD5363, or within 28 days of the subject's last dose of AZD5363, 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 Y specific expedited reporting exceptions:

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

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

3.2.2 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 <u>second malignancy</u> 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.

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3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for AZD5363 (NSC 782347)

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 297 patients*. Below is the CAEPR for AZD5363.

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 2.3, February 28, 2019[1]

Adverse Events with Possible Relationship to AZD5363 (CTCAE 5.0 Term) [n= 297]			**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)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INVESTIGATIONS			
	Creatinine increased		***Creatinine increased (Gr 2)***
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***

Adverse Events with Possible Relationship to AZD5363 (CTCAE 5.0 Term) [n= 297]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RENAL AND URINARY DISORDERS			
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		
Skin and subcutaneous tissue disorders - Other (rash)[2]			***Skin and subcutaneous tissue disorders - Other (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 dry skin, skin fissures, xeroderma, dermatitis exfoliative, exfoliative rash, eyelid exfoliation, skin exfoliation, xerosis, rashes and acnes, rash, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash vesicular, rash follicular, acne pustular, rash pustular, folliculitis, eyelid folliculitis, acne, dermatitis acneiform, drug eruption pruritus, eyelids pruritus, pruritus generalized, erythema, and erythematous rash.

Adverse events reported on AZD5363 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD5363 caused the adverse event:

CARDIAC DISORDERS - Heart failure

GASTROINTESTINAL DISORDERS - Esophageal pain; Gastrointestinal disorders - Other (intestinal obstruction); Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise

INFECTIONS AND INFESTATIONS - Lung infection; Sepsis; Skin infection; Urinary tract infection

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Neutrophil count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Glucose intolerance; Hypercalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

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

NERVOUS SYSTEM DISORDERS - Neuralgia

PSYCHIATRIC DISORDERS - Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Oropharyngeal pain; Pleural effusion; Productive cough

VASCULAR DISORDERS - Thromboembolic event

NOTE: AZD5363 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 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Patients will be monitored closely for toxicity and the dose of AZD5363 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 1a. Dose Levels for AZD5363

Dose Level	Daily Dose/ Route	Dispensed As	Schedule
Starting dose level: 0	480 mg, PO	2 × 200-mg tablets 1 x 80-mg tablet	4 days on/3 days off twice a day on a weekly basis, for each 28 day cycle
–1	400 mg, PO	2 x 200 mg tablet	4 days on/3 days off twice a day on a weekly basis, for each 28 day cycle
–2	320 mg, PO	4 x 80-mg tablets	4 days on/3 days off twice a day on a weekly basis, 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 1b. Dose Levels for AZD5363 for patients continuing fulvestrant or an aromatase inhibitor

Dose Level	Daily Dose/ Route	Dispensed As	Schedule
Starting dose level: 0	400 mg, PO	2 x 200 mg tablet	4 days on/3 days off twice a day on a weekly basis, for each 28 day cycle
–1	320 mg, PO	4 x 80-mg tablets	4 days on/3 days off twice a day on a weekly basis, for each 28 day cycle

If continuing fulvestrant or an aromatase inhibitor, patients requiring more than 1 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 AZD5363
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 AZD5363 delay of > 4 weeks should go off protocol therapy. Growth factor support is allowed, per investigator discretion. Transfuse PRBC as clinically indicated ** Patients requiring > 2 dose reductions of AZD5363 should go off protocol therapy. If continuing fulvestrant or an aromatase inhibitor, patients requiring > 1 dose reductions of AZD5363 should go off protocol therapy.	

Table 3: Non-Hematologic Toxicities (not hyperglycemia or rash)

Grade	Management/Next Dose for AZD5363
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 AZD5363 – 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. If continuing fulvestrant or an aromatase inhibitor, patients requiring > 1 dose reductions of AZD5363 should go off protocol therapy.	
Recommended management of diarrhea: loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used. Recommend management of nausea and vomiting: treat with standard anti-emetics such as prochlorperazine or ondansetron. The use of prophylactic anti-emetics should be considered. Given the potential for ondansetron to increase QTc prolongation, review baseline QTc EKG prior to initiation of ondansetron and consider follow up EKGs on treatment.	

Hyperglycemia

These guidelines are for random blood glucose results. While these grade thresholds are based on CTCAE cut-offs for fasting glucose, they are applied to **random glucose here**. 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 AZD5363-induced hyperglycaemia in diabetic patients include advice from the patient's endocrinologist where appropriate.

For CTC Grade 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 4 are based on those detailed by Busaidy et al[21] for PI3K-AKT-mTOR pathway inhibitors.

Table 4: Hyperglycemia

Grade	Management/Next Dose for AZD5363
Grade 1 (<8.9 mM; OR <160 mg/dL)	No change in dose
Grade 2 (≥8.9 mM and <13.9 mM; OR >160 mg/dL and < 250 mg/dL)	No change in dose. Add or administer a higher dose of oral metformin Consider endocrionology input and home glucose monitoring 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
Grade 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 ≤ Grade 1. Resume at one dose level lower** Immediate endocrionology input and home glucose monitoring Begin 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
Grade 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. polyphagia, polydipsia and polyuria.)	Hold* until ≤ Grade 1. Resume at one dose level lower or discontinue, per investigator discretion** Immediate endocrionology input Consider intravenous fluids and/or admit if hypovolemic signs/symptoms Consider appropriate clinical management of hyperglycaemia per local guidelines (insulin infusion etc.)

* Patients requiring a delay of > 4 weeks should go off protocol therapy.

** Patients requiring > two dose reductions should go off protocol therapy. If continuing fulvestrant or an aromatase inhibitor, patients requiring > 1 dose reductions of AZD5363 should go off protocol therapy.

Table 5: Maculo-Papular Rash

Grade	Management/Next Dose for AZD5363
Grade 1	No change in dose. Initiate dermatological treatment, including topical steroid moderate strength bid and oral anti-histamine, if symptomatic.
Grade 2	No change in dose. No change in dose. Initiate dermatological treatment, including topical steroid moderate strength bid and oral anti-histamine, if symptomatic.
Grade 3	Hold* until ≤ Grade 2. Initiate dermatological treatment, including oral steroid for up to 2 weeks and oral anti-histamine, if symptomatic. If Grade ≤1 and tolerable, reinstate at current dose. If Grade 2 and tolerable, reinstate at one dose level lower. If not tolerable, discontinue AZD5363. **
* Patients requiring a delay of > 4 weeks should go off protocol therapy. ** Patients requiring > two dose reductions should go off protocol therapy. If continuing fulvestrant or an aromatase inhibitor, patients requiring > 1 dose reductions of AZD5363 should go off protocol therapy.	

For those patients with HR positive/HER2 negative metastatic breast cancer who continue to receive anti-estrogen therapy in combination with AZD5363, the anti-estrogen therapy has a distinct toxicity profiles. 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.

For patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1-2 minutes) as one 250-mg injection.

There will be no dose adjustments for aromatase inhibitors. 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 fulvestrant or an aromatase inhibitor, the hormone therapy should be discontinued. However, the patient may remain on the study and continue to take AZD5363.

3.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study. See tables for recommendations of hematologic toxicity (Table 2), non-hematologic toxicity (Table 3: nausea, emesis, diarrhea), hyperglycemia (Table 4), maculo-papular rash (Table 5).

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AZD5363 showed no evidence of phototoxicity so no special precautions are needed by patients with regard to sun exposure or use of sunbeds/tanning booths. However, investigators should be be asked to probe the possibility of phototoxicity when rash AEs are reported.

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

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4.1 Therapeutic Parameters for AZD5363 Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients on AZD5363 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	C1D1, C1D4, and C1D11[L]	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]				X
Performance status	X	X[J]				X
CBC w/diff, plts[B]	X	X[J]	X[L]			X
Serum chemistry[B,O]	X	X[J]	X[L]			X
Urinalysis[B]	X	X[J]	X[L]			
Radiologic evaluation[C]	X			X[C]		X[F]
β-HCG[D]	X					
Toxicity Assessment[E]		X			X	X[F]
Pill Count/Diary[G]		X			X	
ECG	X[H]	X[K]				
Tumor biopsy and blood sample for MATCH Master Protocol[I]				X	X	
Anti-estrogen therapy[M]	X	X[N]				

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

B. 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 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). Urinalysis is without microscopy. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease. Hyperglycemia management is described in Section 3.4.

C. 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.

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

E. 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.

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. 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.

H. Within 8 weeks of treatment assignment.

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

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

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

J. 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; Urinalysis; Concomitant Medications.

K. As clinically indicated.

L. The patient will also return for C1D4 (+/- 1 day) and C1D11 (+/- 1 day) for pre-dose AZD5363 basic metabolic panel (including glucose), CBC w/diff, and urinalysis. It is not required that these labs be collected while the patient is fasting. Hyperglycemia management is described in Section 3.4.

M. 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. Patients who will be continuing fulvestrant or an aromatase inhibitor will be instructed to take AZD5363 400 mg orally daily twice a day, 4 days on/3 days off on a weekly basis for each 28 day cycle. Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg

injection. For the aromatase inhibitor, there is no modification in dosing and patients are NOT allowed to switch within class (for instance, letrozole to anastrazole). GnRH agonists are allowed to continue as previously administered. SERMS, such as tamoxifen or toremifene, are not allowed.

N. If the patient is given Fulvestrant and/or a GnRH agonist, these should be given on D1 of the cycle (+/- 7 days).

O. Fasting Glucose required at screening. Subsequent glucose will be checked with serum chemistry and can be non-fasting, per investigator discretion.

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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.

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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 AZD5363 (NSC 782347)

5.1.1 Other Names: AZD5363

5.1.2 Classification:

Oral AKT inhibitor

5.1.3 Mode of Action:

AZD5363 is a potent, oral inhibitor of kinase activity of serine/threonine specific protein kinase (Akt). AZD5363 inhibits activity of three Akt isoforms (Akt1, Akt2, Akt3), which are activated in different solid tumors. AKT is a hub of multiple signaling pathways promoting tumorigenesis, inhibiting apoptosis, promoting invasion and migration and is often associated with resistance to established cancer therapies. AZD5363 is expected to have efficacy when combined with cytotoxic cancer therapies or other targeted or anti-hormonal agents.

5.1.4 Storage and Stability:

Storage: Store below 30°C.

If a storage temperature excursion is identified, promptly return AZD5363 to below 30°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. Per the manufacturer, if re-packaging in a HDPE pharmacy bottle is necessary, assign the re-packaged bottle a 30-day expiration date.

5.1.5 Dose Specifics:

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Dosing is described in Section 3.4. Starting dose is 480 mg PO BID twice a day on a weekly basis, (4 days on/3 days off) for a 28-day cycle. Patients who will be continuing fulvestrant or an aromatase inhibitor will be instructed to take AZD5363 400 mg orally daily twice a day, 4 days on/3 days off on a weekly basis for each 28 day cycle.

5.1.6 How Supplied:

AstraZeneca supplies and PMB, CTEP, DCTD distributes AZD5363 as beige film-coated tablets in 80 mg and 200 mg strengths. Tablets are packed in high-density polyethylene (HDPE) bottles. Each bottle is secured with a heat induction seal, child-resistant closure and no desiccant.

- 80 mg:7 mm round, biconvex tablets in 30-count bottles
- 200 mg: 9 mm round, biconvex tablets in 60-count bottles

Each tablet contains AZD5363, microcrystalline cellulose, mannitol, croscarmellose cellulose and magnesium stearate. The tablet film-coat contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, yellow iron oxide, red iron oxide and black iron oxide.

5.1.7 Route of Administration:

Oral. Take on an empty stomach at least 2 hours after a meal and 1 hour before the next meal.

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5.1.8 Incompatibilities:

In vitro experiments have demonstrated, AZD5363 to be a substrate of uridine diphosphate glucuronosyl transferase (UGT) 1A9 and 2B7 isoforms, which are responsible for the formation of the glucuronide metabolite. CYP3A4 is mainly responsible for the formation of monooxygenated metabolites, with contributions from CYP2C9 and CYP3A5. Avoid potent inhibitors or inducers of any of these enzyme systems. In particular, the manufacturer advises against the co-administration of potent inhibitors or inducers of CYP 3A4/5 within 2 weeks (3 weeks for St John's Wort) before the first dose of study treatment and until 2 weeks after the last dose of study treatment.

AZD5363 is a substrate for the P-gp transporter in vitro, but not BCRP. There is a potential for increased systemic exposures of AZD5363 by potent P-gp inhibitors.

In vitro experiments indicate that AZD5363 is a reversible inhibitor of CYP3A4/5, 2C9, 2D6 and UGT1A1 and to a lesser extent CYP 2B6 and 2C19, but the agent was found not to be an inhibitor for other CYP isoforms tested (1A2, 2A6, 2C8, 2E1). Avoid co-administration of CYP 3A4/5, 2C9 and 2D6 sensitive substrates in patients from the time they enter screening until 2 weeks after the last dose of study treatment since this may result in increased exposure of these substrates.

AZD5363 is not a significant inducer of CYP3A4/5 enzyme activity and was found to have no effect on activity of CYP 1A1/2, 2B6 or pregnane X receptor (PXR).

In vitro data indicate AZD5363 inhibits the organic anion-transporting polypeptides (OATP1B1 and OATP1B3), OAT3 and MATE2K and therefore suggests there is potential drug-drug interaction with sensitive substrates. These transporters are implicated in the distribution and clearance of many of the statins. Of the statins that are minimally affected by CYP3A4 inhibition and recommended for use in patients receiving AZD5363, rosuvastatin and pravastatin (but not fluvastatin) can be affected by OATP1B1 and OATP1B3 inhibition. Based on current data, the AUC of these drugs may be increased by 1.3-fold for pravastatin and 1.5-fold for rosuvastatin. The manufacturer recommends that doses of rosuvastatin be capped to 10 mg once daily and pravastatin to 40 mg once daily when combined with AZD5363 starting 2 weeks prior and ending 2 weeks after AZD5363 treatment.

AZD5363 is an inhibitor of organic cationic transporter 2 (OCT2) and MATE1. There is a potential for drug-drug interactions with sensitive substrates, such as metformin; therefore, use metformin with caution in patients who are taking AZD5363.

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AZD5363 is not an inhibitor of P-glycoprotein (P-gp) and is not expected to affect sensitive P-gp substrates. This agent is an inhibitor of human efflux transporter breast cancer resistance protein (BCRP), although the risk of causing drug-drug interactions with substrates of this transporter is considered to be low per the manufacturer.

Appropriate medical judgment is required. Refer to Appendix III for a sample list.

5.1.9 Patient Care Implications

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for at least 4 months after the last dose of AZD5363. Men study participants are required to use barrier methods of contraception and avoid sperm donation throughout the study and for 4 months after the last dose of AZD5363.

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It is not known whether the preclinical changes seen in the male animal reproductive organs, after treatment with AZD5363, will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Therefore, if male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

5.1.10 Side Effects

See Section 3.3 for side effects.

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6. Translational Studies

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

7. References

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Appendix I

Patient Pill Calendar

Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of each tablet.
2. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
3. All doses of AZD5363 should be taken with water only, on an empty stomach, no food for at least 2 hours before a dose and for at least 1 hour after.
4. AZD5363 is to be taken twice per day for 4 days in a row followed by 3 days where no AZD5363 is taken.
5. If you vomit after AZD5363 dosing, do not retake new tablet(s), but continue to take the next dose 12 hours later.
6. If you miss a dose, you may take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be made up.
7. If you need to take the dose earlier for whatever reason, you can take the dose up to 2 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.

AZD5363

DAY	Date			Time tablets taken		Number of tablets taken (80 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	AM	PM	AM	PM	AM	PM	
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28										

Patient Signature: _____ Date: _____

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

Rev. 3/17 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.** AZD5363 is taken 4 days on/3 days off. 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.

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				AZD5363						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.)
	Date			Time tablets taken		Number of tablets taken (80 mg)		Number of tablets taken (200 mg)		Time 1 tablet taken		
DAY	Month	Day	Year	AM	PM	AM	PM	AM	PM	AM	PM	
1												
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Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Y: AZD5363 in Patients with Tumors with AKT Mutations

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Appendix II

Actionable Mutations for Sub-Protocol EAY131-Y

List of inclusion variants:

Gene Name	Variant ID	Variant Description	Level of Evidence Code
AKT1	p.E17K	AKT mutation	Level 2A

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List of exclusion variants

Gene Name	Variant ID	Variant Description	Level of Evidence Code
BRAF	MACF1-BRAF.M60B9	Fusion	1
BRAF	TRIM24-BRAF.T9B9.1	Fusion	1
BRAF	SLC12A7-BRAF.S17B11	Fusion	1
BRAF	CLIP2-BRAF.C6B11	Fusion	1
BRAF	KIAA1549-BRAF.K18B9.COSF511	Fusion	1
BRAF	TRIM24-BRAF.T3B11	Fusion	1
BRAF	KIAA1549-BRAF.K15B10.COSF1283.1	Fusion	1
BRAF	CEP89-BRAF.C16B9	Fusion	1
BRAF	ATG7-BRAF.A18B9	Fusion	1
BRAF	RNF130-BRAF.R3B9.COSF1483	Fusion	1
BRAF	SND1-BRAF.S11B11	Fusion	1
BRAF	KLHL7-BRAF.K5B9	Fusion	1
BRAF	ERC1-BRAF.E12B10	Fusion	1
BRAF	AP3B1-BRAF.A22B9	Fusion	1
BRAF	AKAP9-BRAF.A22B9	Fusion	1
BRAF	ARMC10-BRAF.A4B11	Fusion	1
BRAF	KIAA1549-BRAF.K9B9	Fusion	1
BRAF	AGK-BRAF.A2B8	Fusion	1
BRAF	SOX6-BRAF.S6B9	Fusion	1
BRAF	AKAP9-BRAF.A28B9	Fusion	1
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	Fusion	1
BRAF	BRAF-AP3B1.B8A23	Fusion	1
BRAF	GATM-BRAF.G2B11	Fusion	1
BRAF	CCDC6-BRAF.C1B9	Fusion	1
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	Fusion	1

Gene Name	Variant ID	Variant Description	Level of Evidence Code
BRAF	TRIM24-BRAF.T11B2	Fusion	1
BRAF	MZT1-BRAF.M2B11	Fusion	1
BRAF	MKRN1-BRAF.M4B11.COSF1444	Fusion	1
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	1
BRAF	BCL2L11-BRAF.B3B10	Fusion	1
BRAF	ZC3HAV1-BRAF.Z7B11	Fusion	1
BRAF	CUX1-BRAF.C10B9	Fusion	1
BRAF	STRN3-BRAF.S3B10	Fusion	1
BRAF	DYNC1I2-BRAF.D7B10	Fusion	1
BRAF	KCTD7-BRAF.K4B8	Fusion	1
BRAF	SND1-BRAF.S9B9	Fusion	1
BRAF	UBN2-BRAF.U3B11	Fusion	1
BRAF	SND1-BRAF.S10B11	Fusion	1
BRAF	KIAA1549-BRAF.K14B9.COSF483	Fusion	1
BRAF	KIAA1549-BRAF.K12B11	Fusion	1
BRAF	EML4-BRAF.E6B10	Fusion	1
BRAF	GHR-BRAF.G1B10	Fusion	1
BRAF	PAPSS1-BRAF.P5B9.1	Fusion	1
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	1
BRAF	FAM114A2-BRAF.F9B11	Fusion	1
BRAF	TMEM178B-BRAF.T2B9	Fusion	1
BRAF	RBMS3-BRAF.R11B11	Fusion	1
BRAF	AGAP3-BRAF.A9B9	Fusion	1
BRAF	FAM131B-BRAF.F1B10.COSF1191	Fusion	1
BRAF	GTF2I-BRAF.G4B10	Fusion	1
BRAF	SND1-BRAF.S18B10	Fusion	1
BRAF	HERPUD1-BRAF.H4B7	Fusion	1
BRAF	TRIM24-BRAF.T10B9	Fusion	1
BRAF	KDM7A-BRAF.K11B11	Fusion	1
BRAF	RAD18-BRAF.R7B10	Fusion	1
BRAF	BRAF-MACF1.B8M15	Fusion	1
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	Fusion	1
BRAF	KIAA1549-BRAF.K14B11.COSF1226	Fusion	1
BRAF	SND1-BRAF.S14B9	Fusion	1
BRAF	C7orf73-BRAF.C2B9	Fusion	1
BRAF	CDC27-BRAF.C16B9.1	Fusion	1

Gene Name	Variant ID	Variant Description	Level of Evidence Code
BRAF	TANK-BRAF.T4B9	Fusion	1
BRAF	LSM14A-BRAF.L9B9	Fusion	1
BRAF	CLCN6-BRAF.C2B11.COSF1440	Fusion	1
BRAF	MKRN1-BRAF.M4B9	Fusion	1
BRAF	ERC1-BRAF.E17B8	Fusion	1
BRAF	TMPRSS2-BRAF.T3B11	Fusion	1
BRAF	KIAA1549-BRAF.K16B10	Fusion	1
BRAF	CCDC91-BRAF.C11B9	Fusion	1
BRAF	KIAA1549-BRAF.K15B9.COSF481.1	Fusion	1
BRAF	KIAA1549-BRAF.K15B11.COSF485.1	Fusion	1
BRAF	KIAA1549-BRAF.K12B9.COSF1474	Fusion	1
BRAF	MYRIP-BRAF.M16B9	Fusion	1
BRAF	LSM12-BRAF.L3B9	Fusion	1
BRAF	TRIM24-BRAF.T3B10	Fusion	1
BRAF	PLIN3-BRAF.P1B9	Fusion	1
BRAF	NUDCD3-BRAF.N4B9	Fusion	1
BRAF	GNAI1-BRAF.G1B10.COSF1442	Fusion	1
BRAF	BBS9-BRAF.B19B4	Fusion	1
BRAF	CUL1-BRAF.C7B9	Fusion	1
BRAF	BAIAP2L1-BRAF.B12B9	Fusion	1
BRAF	AKAP9-BRAF.A7B11	Fusion	1
BRAF	KIAA1549-BRAF.K13B9	Fusion	1
BRAF	AKAP9-BRAF.A21B10	Fusion	1
BRAF	SND1-BRAF.S16B9.1	Fusion	1
BRAF	CCNY-BRAF.C1B10	Fusion	1
BRAF	FXR1-BRAF.F13B10	Fusion	1
BRAF	ZKSCAN5-BRAF.Z2B9	Fusion	1
BRAF	BRAF-CIITA.B9C6	Fusion	1
BRAF	NUB1-BRAF.N3B9	Fusion	1
BRAF	SND1-BRAF.S14B11	Fusion	1
BRAF	KCTD7-BRAF.K3B8	Fusion	1
BRAF	BRAF-SUGCT.B1S13	Fusion	1
BRAF	BRAF-MRPS33.B1M2	Fusion	1
BRAF	ZC3HAV1-BRAF.Z3B10	Fusion	1
BRAF	TAX1BP1-BRAF.T8B11.1	Fusion	1
BRAF	TRIM24-BRAF.T5B8	Fusion	1
BRAF	SOX6-BRAF.S5B9	Fusion	1
BRAF	AGAP3-BRAF.A10B11	Fusion	1

Gene Name	Variant ID	Variant Description	Level of Evidence Code
BRAF	NUP214-BRAF.N21B10	Fusion	1
BRAF	MAD1L1-BRAF.M16B9	Fusion	1
BRAF	RP2-BRAF.R3B10	Fusion	1
BRAF	SND1-BRAF.S10B9	Fusion	1
BRAF	ZSCAN30-BRAF.Z3B10	Fusion	1
BRAF	EPS15-BRAF.E22B10	Fusion	1
BRAF	BTF3L4-BRAF.B3B11	Fusion	1
BRAF	FAM131B-BRAF.F3B9.COSF1193	Fusion	1
BRAF	BRAF-SLC26A4.B3S7	Fusion	1
BRAF	FCHSD1-BRAF.F13B9.COSF403	Fusion	1
BRAF	MAD1L1-BRAF.M17B10	Fusion	1
BRAF	TRIM4-BRAF.T6B10	Fusion	1
BRAF	RNF11-BRAF.R1B11	Fusion	1
BRAF	SND1-BRAF.S9B2	Fusion	1
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

Gene Name	Variant ID	Variant Description	Level of Evidence Code
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
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
KRAS	COSM522	KRAS mutation	p.G12A

Gene Name	Variant ID	Variant Description	Level of Evidence Code
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
NRAS	COSM585	NRAS mutation	p.Q61H
NRAS	COSM586	NRAS mutation	p.Q61H

Molecular Analysis for Therapy Choice (MATCH)
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Appendix III

CYP3A4 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. The Principal Investigator should be alerted if the subject is taking any agent on these lists. Appropriate medical judgment is required.

CYP3A4 Inducing Agents:

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

CYP3A4 Potent Inhibitors:

Phenobarbital
Carbamazepine
Phenytoin
Rifampicin
Rifabutin
Mitotane
Enzalutamide
St John's Wort

CYP2D6 Sensitive Substrates:

Amitryptyline
Atomoxetine
Cenlafaxine
Desipramine
Dextromethorphan
Doxepin
Metoprolol
Venlafaxine
Nebivolol
Nefazodone
Paroxetine
Perphenazine
Trimipramine
Tolterodine
Tropisetron

CYP2D6 Substrates with Narrow Therapeutic Range:

Thioridiazine

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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
GDC-0068	Genentech	ipatasertib	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
AZD-5363	AstraZeneca		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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MATCH Treatment Subprotocol Y: AZD5363 in Patients with Tumors with AKT Mutations

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Appendix V

Information On Possible Drug Interactions

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **AZD5363**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

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

AZD5363 interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- Some of the enzymes in question are UGT 1A9, 2B7 and CYP 3A4/5 and 2C9. AZD5363 is broken down by these enzymes and is affected by other drugs that are potent inducers or inhibitors of UGT 1A9, 2B7 and CYP 3A4/5 and 2C9. Avoid use of other drugs that are strong inducers or inhibitors of these enzymes within 2 weeks (within 3 weeks for St John's Wort) of AZD5363 administration.
- AZD5363 may affect other drugs by inhibiting enzymes needed to clear them from the body. These enzymes are UGT1A1, CYP 3A4/5 and 2D6. Avoid use of other drugs that are sensitive substrates of CYP 3A4/5 and 2D6 within 2 weeks of AZD5363 administration.
- The transport proteins in question are OATP1B1, OATP1B3, OAT3, MATE1, MATE2K, OCT2 and BCRP. AZD5363 may inhibit other drugs from being moved in and out of cells/organs by these transport proteins. In particular, metformin and certain statins may interact with AZD5363 and need to be managed carefully in patients taking them concurrently. Inhibitors of P-gp may affect how AZD5363 is transported in and out of cells/organs.

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

AZD5363 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

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

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

AZD5363 must be used very carefully with other medicines that affect P-gp transporter, UGT 1A9, 2B7 and CYP 3A4/5, 2C9 enzymes needed to clear it from your body. AZD5363 may affect enzymes UGT1A1, CYP 3A4/5 and 2D6 that are needed to clear other drugs from your body. AZD5363 inhibits OATP1B1, OATP1B3, OAT3, MATE1, MATE2K, OCT2 and BCRP transport proteins that may be required to move other drugs in and out of cells/organs. Before you enroll

onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of P-gp, UGT 1A9, 2B7 and CYP 3A4/5, 2C9 or substrates of CYP 3A4/5 and 2D6 or substrates of transport proteins OATP1B1, OATP1B3, OAT3, MATE1, MATE2K, OCT2 and BCRP."

- Please be very careful! Over-the-counter drugs (including herbal supplements such as St John's Wort) 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 ingesting grapefruit juice, grapefruit and Seville oranges while taking AZD5363
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **AZD5363**. This clinical trial is sponsored by the NCI. AZD5363 may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement

AZD5363 interacts with UGT1A1, UGT1A9, 2B7 and CYP 3A4/5, 2C9 and 2D6 and transport proteins P-gp, OATP1B1, OATP1B3, OAT3, MATE1, MATE2K, OCT2 and BCRP and must be used very carefully with other medicines that interact with these enzymes and transport proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of P-gp, UGT 1A9, 2B7 and CYP 3A4/5, 2C9 or substrates of CYP 3A4/5, 2D6 or substrates of transport proteins OATP1B1, OATP1B3, OAT3, MATE1, MATE2K, OCT2 and BCRP."
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking AZD5363.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.

Your study doctor's name is _____

and can be contacted at _____.