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-Z1I, *Phase II Study of AZD1775 in Patients with Tumors Containing BRCA1 and BRCA2 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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.]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. Charles Kunos's June 19, 2019 Request for Rapid Amendment for AZD1775 (adavosertib).

The following revisions to EAY131-Z1I protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version date.
2.	3.3	Updated the AZD1775 (adavosertib) CAEPR list with version 2.6, May 14, 2019.

The following revisions to EAY131-Z1I 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 AZD1775 (adavosertib) possible risks risk list with version 2.6 May 14, 2019.

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

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617.589.0914 ecog-acrin.org

We request review and approval of this addendum to EAY131-Z1I so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Enclosure

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

EAY131-Z1I

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Z1I: Phase II Study of AZD1775 in Patients with Tumors Containing BRCA1 and BRCA2 Mutations

AZD1775 TREATMENT SUBPROTOCOL CHAIR: Shivaani Kummar, MD
AZD1775 TREATMENT SUBPROTOCOL CO-CHAIR: Kim A. Reiss Binder, MD
AZD1775 TRANSLATIONAL CHAIR: James M. Ford, MD

Version Date: July 10, 2019

NOTE: This subprotocol (EAY131-Z1I) should be used in conjunction with the MATCH Master Protocol (EAY131).

SUBPROTOCOL ACTIVATION DATE
March 13, 2017 (Incorporated in Addendum #7)
Addendum #13
Addendum #14
Addendum #17
Addendum #21

Agent		**NSC#**	**Supply**
AZD1775		751084	NCI Supplied

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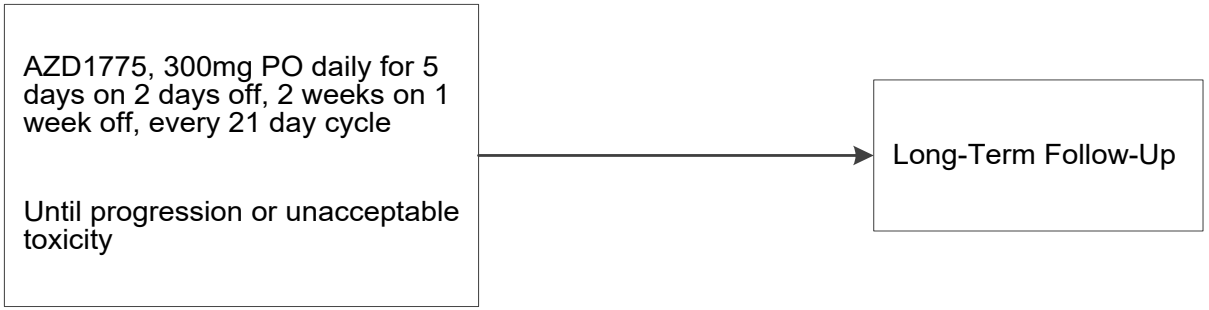
Schema



Cycle = 21 days
Accrual Goal: 35

1. Introduction

1.1 AZD1775

Cell cycle regulation depends on a delicate balance between cyclins and cyclin-dependent kinases (Cdks) that allow for progression through the cell cycle, and Cdk inhibitors that halt progression in the setting of DNA damage. DNA replication during S phase generates intermediate DNA structures that are vulnerable to genotoxic insults. In addition, oncogenes can induce lesions at replication forks, further exacerbating genomic instability. In response to DNA damage, surveillance protein complexes such as Mre11/Rad50-Nbs1 complex and Rad9/Rad1/Hus1 complex recruit repair proteins and halts cell cycle progression, allowing time for DNA repair. Ataxia-telangectasia mutated (ATM) protein kinase and ataxia-telangectasia-related (ATR) protein kinase, two members of the phosphatidyl inositol 3-kinase-like kinase (PIKK) family, are central to the DNA damage repair process. Depending on the type of genotoxic stress, either ATM or ATR is preferentially activated[1]. ATM is primarily activated in response to double-stranded DNA breaks, while ATR is activated by a broader spectrum of genotoxic stimuli and primarily activated in response to single-strand DNA breaks.

ATM/ATR kinases regulate cell cycle checkpoints by phosphorylation of multiple downstream proteins, including proteins associated with the recognition of double-stranded DNA breaks such histone H2AX, proteins involved in the assembly of protein complexes at the site of DNA damage, and effector kinases such as checkpoint kinase 1/2 (Chk1) and (Chk2). In contrast to Chk2, Chk1 can be activated by both ATM and ATR, and activation can occur during normal cell cycle progression or in response to replicative stress. Activated Chk1 in turn concomitantly phosphorylates Wee1 and Cdc25C, thereby activating Wee1 kinase activity and inactivating Cdc25C phosphatase activity. Wee1 is a tyrosine kinase implicated in the inhibitory phosphorylation of CDK1/CDC2-bound cyclin B complex responsible for G2 arrest. Originally identified in fission yeast, wee 1 deficiency resulted in premature mitotic entry and replication of smaller-sized yeast. Wee1 belongs to a family of protein kinases involved in the terminal phosphorylation and inactivation of (CDK1/CDC2)-bound cyclin B via phosphorylation of its Tyr15 residue near the ATP-binding pocket, resulting in G2 cell cycle arrest in response to DNA damage. Wee1 overexpression has been demonstrated in hepatocellular carcinoma, luminal and HER-2 positive breast cancers, colon, lung carcinoma, and seminoma tumor samples.

AZD1775, 2-allyl-1-[6-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-6-[4-

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(4-methylpiperazin-1-yl)anilino]pyrazolo[3,4-d]pyrimidin-3-one hemihydrate, is a selective, adenosine-triphosphate (ATP) competitive, small molecule inhibitor of Wee1 kinase (IC_{50} = 5.18nM), that directly inhibits phosphorylation of CDC2 at Tyr15. A comprehensive review of AZD1775 can be found in the AZD1775 Investigator's Brochure.

AZD1775 has been shown to inhibit phosphorylated CDC2 in p53 mutant WiDr colon and lung carcinoma cells, as measured by colorimetric ELISA in a dose-dependent manner [Figure 1A]. Additionally, premature mitotic entry was demonstrated by concomitant increase in the percentage of cells expressing phosphorylated histone H3 at the same doses [Figure 1B].

Figure 1A

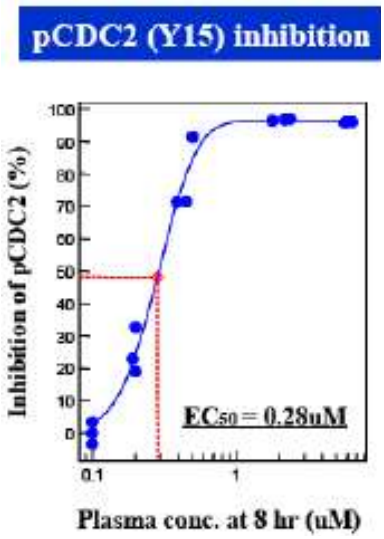
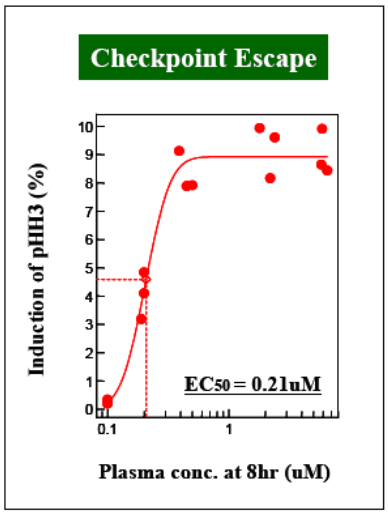


Figure 1B



In *in vitro* studies, AZD1775 inhibits WEE1 activity and induces DNA damage as well as G2/M checkpoint escape in cell-based assays. AZD1775 increases cytotoxicity when used in combination with DNA damaging agents, such as gemcitabine, cisplatin, carboplatin, and topotecan, in p53-deficient cell lines. In *in vivo* studies, AZD1775 was well tolerated and showed enhancement of anti-tumor efficacy by gemcitabine, carboplatin, cisplatin, 5-fluorouracil (5-FU), and capecitabine in nude rat xenograft tumor models. Similarly, in nude mouse xenograft models, AZD1775 treatment resulted in significant tumor growth inhibition at tolerated doses, and also enhanced the anti-tumor growth effect of gemcitabine, carboplatin, radiation therapy, and olaparib, a PARP inhibitor that also induces replication associated DNA damage. Moreover, in preclinical cancer cell models associated with high levels of endogenous replication stress resulting from a combination of G1/S checkpoint deficiencies due to p53 mutations or CDKN2A deletions and the over-expression of oncogenic drivers such as MYC, mutant KRAS or the amplification of Cyclin E, AZD1775 also demonstrated significant single-agent anti-tumor activity.

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1.2 Supporting Preliminary Data

As of 11 November 2016, a total of approximately 551 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. In addition, approximately 350 patients have also received AZD1775 as part of externally-sponsored scientific research. These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose in combination with chemotherapy, and 325 mg twice a day (BID) in a multiple-dose regimen in combination with chemotherapy.

The PK data of AZD1775 following a single oral administration showed a moderate rate of absorption with a Tmax occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a t1/2 in the region of 10 hours. Exposure as measured by maximum plasma drug concentration observed (Cmax) and AUC0-∞ increased in a dose-proportional manner over the dose range of 325 to 1300 mg.

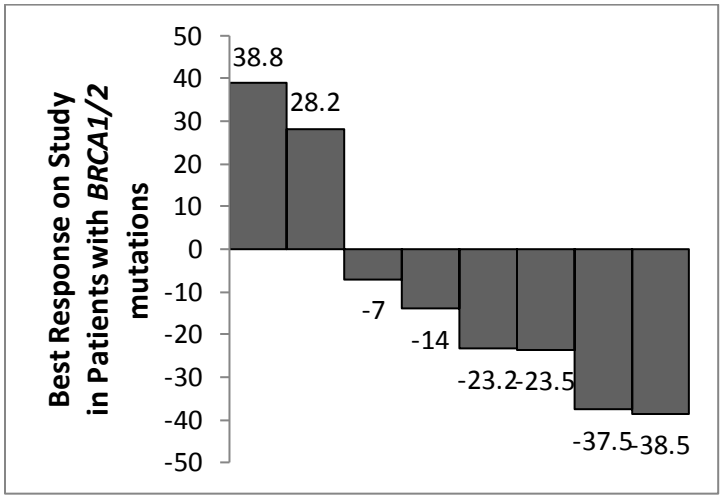
Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies adverse drug reactions to AZD1775 monotherapy include: anemia, neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite.

Based on information emerging during the clinical development program of AZD1775, potential risks with AZD1775 monotherapy include asthenia/fatigue, febrile neutropenia, gastrointestinal hemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation.

Based on the safety data from the 6 completed clinical studies and preliminary data from ongoing studies, the following have been determined to be important identified and/or potential risks, and should be closely monitored: blood and lymphatic disorders (anaemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia, febrile neutropenia, pancytopenia), gastrointestinal disorders (diarrhoea, vomiting, nausea), and cardiac disorders (tachycardia, palpitations, QTc prolongation). Gastrointestinal haemorrhage is also included as an important potential risk.

The inhibition of WEE1 results in perpetually active CDK-1-Cyclin-B, leading to dysregulation of the G2 checkpoint and ongoing cell mitosis despite aberrancies in the DNA. Cells deficient in HR repair secondary to mutations in the BRCA genes have defective DNA damage repair. Inhibition of WEE 1 kinase in such cells would result in a higher fraction of cells with defective DNA entering mitosis, eventually leading to apoptosis. This was demonstrated in the single agent trial of AZD1775 in patients with advanced solid tumors[2]. Nine patients with *BRCA1/2* mutations were enrolled in this study, 2 in the escalation phase and 7 in the *BRCA* expansion cohort. Confirmed partial responses were observed in two patients with germline *BRCA1* mutations, one with a deletion in exon 15 and another with a mutation in the coding region of exon 11 (C3508G). [Figure 2]

Figure 2: Clinical responses in patients carrying BRCA mutations enrolled on the single agent AZD1775 study



In order to evaluate for the pharmacodynamics effects of the tumor, six patients were enrolled in the expansion cohort with paired tumor biopsies obtained at

baseline and 2 to 5 hours after the fifth dose of the first week of administration of drug. Five of 6 paired tumor biopsies showed adequate tumor content and were considered analyzable for pharmacodynamic endpoints. Dramatic reductions in pY15-Cdk levels (84% and 90% compared to baseline) were found in 2 of 5 paired tumor biopsies with 3 of the 5 patients also demonstrating concurrent evidence of DNA damage response based on increased levels of γH2AX [Figure 3]. We were unable to detect a decrease in pY15-Cdk for one patient specimen due to low expression of pY15-Cdk at baseline. One patient with *KRAS*-mutant non-squamous non-small cell lung cancer (NSCLC) with *TP53* mutation on archival tissue had a concurrent increase in pHH3 level as well as γH2AX level on post-treatment tumor biopsy[Figure 3].

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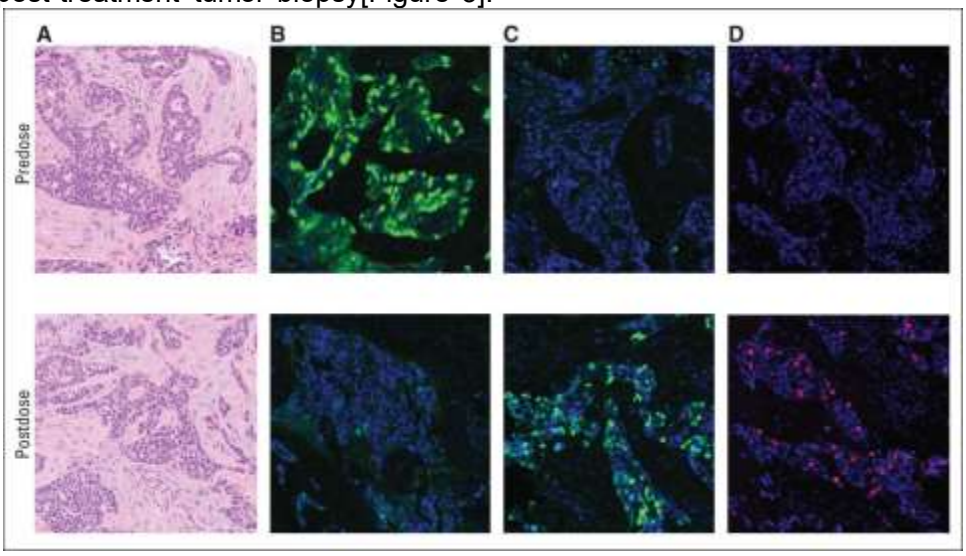

Figure 3: Reduction in pY15-Cdk and concurrent increase in gH2AX signaling and pHH3 by AZD1775 in paired tumor biopsies: Immunofluorescence assay for pY15-Cdk (phosphorylated Tyr15-Cdk), γH2AX (phosphorylated histone H2AX), and pHH3 (phosphorylated histone H3) in paired tumor biopsies from a patient with nonsquamous non–small-cell lung carcinoma. Post-treatment biopsies were obtained 2 to 5 hours after the fifth dose on day 3 of cycle 1. Hematoxylin and eosin staining demonstrates adequate tumor content. A decrease in pY15-Cdk signal in the post-treatment biopsy is consistent with the downstream effect of Wee1 inhibition. Increases in γH2AX and pHH3 levels were observed in the post-treatment biopsy. (A) Hematoxylin and eosin, (B) pY15-Cdk, (C) γH2AX, and (D) pHH3.

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 Registration to Treatment

_____ 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 mutation in the BRCA1 or BRCA2 gene in the tumor, or another aberration, as determined via the MATCH Master Protocol and according to Appendix II. See Appendix II for information on the targeted mutations and corresponding Levels of Evidence. Patients with tumor carrying mutations defined as variants of uncertain significance will not qualify.

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_____ 2.1.3 Patients with ovarian cancer or HER2 negative, metastatic breast cancer must have received a PARP inhibitor as part of or as one of their prior lines of therapy.

_____ 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: _____

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_____ 2.1.5 Patients must not have known hypersensitivity to AZD1775 or compounds of similar chemical or biologic composition.

_____ 2.1.6 Patients receiving any medications or substances that are inhibitors or inducers of CYP3A4, or CYP3A4 substrates need to be reviewed by the study investigator (Appendix VI MATCH Master Protocol). Continuation of such medications will be at the discretion of the study investigator. Concomitant use of aprepitant and fosaprepitant is prohibited. Please refer to Section 5.1.8 for more information.

_____ 2.1.7 Patients have hemoglobin (HgB) ≥ 9 g/dL, which should be done ≤ 4 weeks prior to registration to treatment step.

_____ 2.1.8 Resting corrected QTc interval using the Fridericia formula (QTcF) should be < 450 msec/male and < 470 msec/female (as calculated per institutional standards) obtained from electrocardiogram (ECG), prior to enrollment. If resting QTc interval using the Fridericia formula (QTcF) is > 450 msec/male and > 470 msec/female (as calculated per institutional standards), then 2 additional ECGs should be performed 2-5 minutes apart at study entry. In order to be eligible, the mean resting corrected QTc interval using the Fridericia formula (QTcF) should be < 450 msec/male and < 470 msec/female (as calculated per institutional standards).

_____ _____

Physician Signature Date

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

3. AZD1775 Treatment Plan

3.1 Administration Schedule

AZD1775 capsules will be administered orally, 300 mg once daily for 5 days on 2 days off, 2 weeks on 1 week off, per cycle. Each cycle is 21 days. Patients will be asked to maintain a Study Medication Diary/pill calendar (Appendix I) and record each dose of medication. Patients will be given instructions for completing the pill calendar and will be asked to return it to the clinic staff at the end of each cycle. Cycles will be repeated until disease progression or as noted in Section 3.6. Radiologic assessment of disease status will be performed every 3 cycles.

Since there is a potential for interaction of AZD1775 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

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.

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3.2.1 Additional instructions, requirements and exceptions for protocol EAY131 – Subprotocol Z1I

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 Z1I 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 AZD1775, or within 28 days of the female patient's last dose of AZD1775, 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 Z1I specific expedited reporting exceptions:

For Subprotocol Z1I, 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 second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

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

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

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

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

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Rev. Add17
Rev. Add21

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for AZD1775 (MK-1775, NSC 751084)

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 313 patients*. Below is the CAEPR for AZD1775 (MK-1775, NSC 751084).

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.

Version 2.6, May 14, 2019[1]

Adverse Events with Possible Relationship to AZD1775 (adavosertib) (CTCAE 5.0 Term) [n= 313]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Febrile neutropenia	
CARDIAC DISORDERS			
		Atrial fibrillation	
		Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
		Gastrointestinal hemorrhage[2]	
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatitis)	
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[3] (Gr 3)***
INVESTIGATIONS			

Adverse Events with Possible Relationship to AZD1775 (adavosertib) (CTCAE 5.0 Term) [n= 313]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		***Back pain (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Hypoxia	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[4]		***Rash[4] (Gr 2)***
VASCULAR DISORDERS			
		Phlebitis	

[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]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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

[4]Rash may include rash, erythema, eczema, and rash maculo-papular.

[5]Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy.

[6]Acute kidney injury includes renal impairment and acute renal insufficiency.

Adverse events reported on AZD1775 (adavosertib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD1775 (adavosertib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (thrombocytosis); Leukocytosis

CARDIAC DISORDERS - Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Ear pain; Hearing impaired; Tinnitus

EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (eye swelling); Eye pain; Keratitis; Photophobia; Scleral disorder; Vision decreased; Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Belching; Bloating; Cheilitis; Colitis; Colonic obstruction; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Flatulence; Gastric ulcer; Gastritis; Hemorrhoids; Oral pain; Rectal pain; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter site pain); Infusion site extravasation; Malaise; Non-cardiac chest pain; Pain

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (excoriation); Injury, poisoning and procedural complications - Other (ligament sprain)

INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; GGT increased; Investigations - Other (blood urea increased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Alkalosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Flank pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (groin pain); Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoid tumor); Tumor pain

NERVOUS SYSTEM DISORDERS - Central nervous system necrosis; Cognitive disturbance; Dysesthesia; Dysgeusia; Encephalopathy; Lethargy; Nervous system disorders - Other (hemiparesis); Paresthesia; Peripheral neuropathy[5]; Presyncope; Somnolence; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression

RENAL AND URINARY DISORDERS - Acute kidney injury[6]; Hematuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema; Reproductive system and breast disorders - Other (female genital tract fistula)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Epistaxis; Hiccups; Nasal congestion; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (diaphragmalgia); Voice alteration; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin ulceration; Urticaria

VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event

NOTE: AZD1775 (adavosertib) 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).

Toxicities should have resolved to ≤Grade 2 prior to starting the next cycle. Treatment may be delayed for a maximum of 2 weeks beyond the actual cycle length of 21 days for toxicities that develop and do not resolve as defined above. Beyond two weeks, the patient will not receive further therapy on this protocol and will be followed for resolution of toxicities.

Treatments may be delayed up to 7 days past the end of the previous cycle of 21 days for scheduling conflicts at the discretion of the investigator.

Patients will be allowed up to 2 dose reductions. If more than 2 dose reductions are required, the patient will be removed from the study.

3.4.1 Dose Reduction:

Dose Level	Unit dose
-1	200 mg
-2	175 mg

Dosing regimen will remain as AZD1775 capsules administered orally for a total of 10 doses, 300 mg PO daily for 5 days on and 2 days off, 2 weeks on and 1 week off, every 21 day cycle.

Dose modifications are defined below: No dose interruptions or modifications will be made for any grade alopecia or lymphopenia.

3.4.2 **Grade 2 Drug-related toxicity:** No changes will be made to the dose of AZD1775 for Grade 2 toxicities. Therapy will not be interrupted for Grade 2 hematologic toxicities.

3.4.3 **Grade 3-4 Drug-related non-hematologic toxicities:** Doses of AZD1775 will be held until toxicities recover to ≤ Grade 2 prior to re-initiating treatment at the next lower dose level. Electrolyte abnormalities will not require dose reduction if resolution to Grade 2 or less is documented within 72 hours. Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment (See Section 3.5).

3.4.4 **Grade 3 Drug-related hematologic toxicities:** Dose of AZD1775 will be held until hematologic toxicities, except lymphopenia, or leukopenia in the absence of neutropenia, have resolved to ≤ Grade 2 prior to re-initiating treatment at the same dose level.

3.4.5 **Grade 4 Drug-related Hematologic Toxicities:** Dose of AZD1775 will be held until hematologic toxicities, except lymphopenia, or leukopenia in the absence of neutropenia, have resolved to ≤ Grade 2 prior to re-initiating treatment at the next lower dose level.

3.5 Supportive Care

3.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

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3.5.2 Nausea/Vomiting

All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO QD or granisetron (Kytril) 1 mg PO QD prior to each dose of AZD1775. If nausea and vomiting continue, a second dose of antiemetics can be taken 8 hours later if necessary. In addition, dexamethasone 4 mg PO may be given prior to each AZD1775 dose in cases of continued nausea/vomiting unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed.

Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.

Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs.

Patients should be strongly encouraged to maintain liberal oral fluid intake.

Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

3.5.3 Diarrhea

If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po with every 2 hours (4 mg every 4 hours while asleep), until resolution of episode for at least 12 hours (no more than 16 mg of loperamide during a 24-hour period). This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours ≤ to Grade 2 with the above regimen (maximum of 16 mg of loperamide in a 24-hour period). If the patient develops blood or mucus in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, anti-diarrheals will be discontinued and the patient will be treated with IV fluids and antibiotics as medically indicated.

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3.5.4 Neutropenia

Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

3.5.5 Anemia

Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (http://www.asco.org).

3.5.6 Thrombocytopenia

Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤ 10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm3.

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 AZD1775 Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving AZD1775 treatment.

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

Test/Assessment	Prior to Registration to Treatment	Treatment		End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Every 3 Cycles		
H&P, Weight, Vital signs[A]	X	X[I]			X
Performance status	X	X[I]			X
CBC w/diff, plts[B]	X	X[I]			X
Serum chemistry[B]	X	X[I]			X
Hemoglobin	X				
Radiologic evaluation[D]	X		X[D]		X[F]
Rev. Add13 β-HCG[C]	X	X			
Toxicity Assessment[G]		X		X	X[F]
Pill Count/Diary[H]		X		X	
ECG[J]	X	X			
Rev. Add13 Tumor biopsy and blood sample for MATCH Master Protocol[E]			X	X	

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

Rev. Add13 B. 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). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

Rev. Add13 C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment and prior to the start of each cycle.

Rev. Add13 D. Disease measurements are repeated every 3 cycles 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.

Rev. Add13 E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

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

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

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

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

H. 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.

Rev. Add13 I. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

J. Within 8 weeks of treatment assignment.

Rev. Add13 **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 AZD1775 (NSC 751084)

5.1.1 Other Names

MK-1775

5.1.2 Classification

Inhibitor of WEE1 kinase

5.1.3 Mode of Action

AZD1775 inhibits WEE1 which phosphorylates and inhibits cyclin-dependent kinases 1 (CDK1) and 2 (CDK2), and is involved in regulation of the intra-S and G2 cell cycle checkpoints. In in vitro and in vivo preclinical models, AZD1775 selectively enhanced chemotherapy induced death of cells deficient in p53 signaling.

5.1.4 Storage and Stability

Storage: Store at 2 to 30˚C (36 to 86˚F). Do not freeze.

Stability: Shelf-life stability studies of AZD1775 capsules are ongoing.

5.1.5 Dose Specifics

AZD1775 capsules will be administered orally for a total of 10 doses, 300 mg once daily for 5 days on and 2 days off, 2 weeks on and 1 week off, every 21 day schedule

Rev. Add17 5.1.6 Preparation

AZD1775 is supplied by AstraZeneca and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as capsules available in 25 mg (yellow color, size 2 gelatin capsule) and 100 mg (orange color, size 2 gelatin capsule) strengths. The dry-filled capsules consist of a roller-compacted granule of drug substance, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Each high density polypropylene (HDPE) bottle contains 20 capsules.

5.1.7 Route of Administration

Oral administration. Take AZD1775 two hours before a meal or two hours after a meal. Capsules should not be opened.

5.1.8 Incompatibilities

AZD1775 is primarily metabolized by CYP3A4 and is a weak, time-dependent inhibitor of CYP3A4. Avoid concomitant CYP3A4 moderate or strong inhibitors/inducers, and sensitive substrates with a narrow therapeutic index. AZD1775 is also a weak inhibitor of CYP2C19. Caution should be exercised with concomitant administration of sensitive substrates or substrates with a narrow therapeutic index.

In vitro transporter studies have shown that AZD1775 was an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and a substrate for P-gp and BCRP. The PK parameters of AZD1775 could be altered if AZD1775 is coadministered with P-gp and BCRP inhibitors/inducers, and there is potential for drug-drug interactions when coadministered

with OATP1B1, OATP1B3, MATE1, MATE2K, P-gp and BCRP substrates. This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of atorvastatin when coadministered with AZD1775 and the use of atorvastatin is therefore prohibited.

5.1.9 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.

Specifically, for patients enrolled in this subprotocol:

We will plan to use banked blood on all eligible patients enrolled to perform correlative germline DNA genetic studies. We plan to perform germline panel sequencing on these samples for the proposed genes of interest and correlate these findings with clinical outcomes to determine whether the origin of the driver mutation (germline vs. somatic) alters response rates. Furthermore, we will request tumor samples from the eligibility biopsies to perform additional somatic genomic profiling, including confirming loss-of-heterozygosity for the target DNA repair gene, and an assessment of overall genomic instability. Finally, when available, we will analyze re-biopsy samples from patients responding and then relapsed for mechanisms of drug resistance. These include reversion mutations of the target genes (e.g. BRCA1, 2), mutations in the target enzyme Wee1 kinase, or additional secondary genomic alterations.

The analyses will be performed for research purposes only, on clinically annotated but de-identified samples. None of these results will be reported to the patients or their families.

7. References

1. Santo L, Siu KT, Raje N. Targeting Cyclin-Dependent Kinases and Cell Cycle Progression in Human Cancers. Semin Oncol. 2015 Dec;42(6):788-800
2. Do K, Wilsker D, Ji J, et al. Phase I Study of Single-Agent AZD1775 (MK-1775), a Wee1 Kinase Inhibitor, in Patients with Refractory Solid Tumors. J Clin Oncol. 2015 Oct 20;33(30):3409-15

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1I: AZD1775, BRCA Mutations

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Appendix I

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each capsule.
2. If you forget, the missed capsules will not be taken later.
3. Please bring the empty bottle or any leftover capsules and your pill calendar to your next clinic visit.
4. You will take AZD1775 by mouth once a day on days 1-5 and 8-12 for a total of ten doses every 21 days. The drug is given in cycles; each cycle is 21 days long.
5. Take AZD1775 on an empty stomach, two hours before a meal or two hours after a meal.
6. Capsules should be swallowed whole.
7. Store AZD1775 at room temperature.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules 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 capsules and your completed pill calendar to your doctor's visits.

AZD1775

DAY	Date			Time pills taken	Number of pills taken	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						
21						

Molecular Analysis for Therapy Choice (MATCH)
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Appendix II

Actionable Mutations for Sub-Protocol EAY131-Z1I

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Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
BRCA2	CV51385	SNV	p.Met1Arg	3
BRCA2	CV37871	SNV	p.Met1Ile	3
BRCA2	CV51711	SNV	p.Val159Met	3
BRCA2	CV51708	SNV	splicesite	3
BRCA2	CV37923	SNV	splicesite	3
BRCA2	CV52058	SNV	p.Val211Ile	3
BRCA2	CV38035	SNV	p.Val211Leu	3
BRCA2	CV236264	SNV	splicesite	3
BRCA2	CV52242	SNV	p.Arg2336Leu	3
BRCA2	CV52241	SNV	p.Arg2336Pro	3
BRCA2	CV52246	SNV	splicesite	3
BRCA2	CV52362	SNV	splicesite	3
BRCA2	CV38110	SNV	splicesite	3
BRCA2	CV38125	SNV	p.Trp2626Cys	3
BRCA2	CV52430	SNV	p.Ile2627Phe	3
BRCA2	CV52455	SNV	p.Arg2659Thr	3
BRCA2	CV52462	SNV	p.Glu2663Val	3
BRCA2	CV52471	SNV	p.Ser2670Leu	3
BRCA2	CV9340	SNV	p.Thr2722Arg	3
BRCA2	CV52515	SNV	p.Asp2723His	3
BRCA2	CV38141	SNV	p.Asp2723Gly	3
BRCA2	CV52535	SNV	p.Gly2748Asp	3
BRCA2	CV52602	SNV	splicesite	3
BRCA2	CV38198	SNV	splicesite	3
BRCA2	CV52712	SNV	splicesite	3
BRCA2	COSM185479	SNV	p.Arg3052Trp	3
BRCA1	CV55611	SNV	p.Val1838Glu	3
BRCA1	CV125857	SNV	splicesite	3
BRCA1	CV55588	SNV	p.Ala1823Thr	3
BRCA1	COSM436662	SNV	p.Gly1788Val	3
BRCA1	CV55548	SNV	p.Cys1787Ser	3
BRCA1	CV236263	Complex	splicesite	3
BRCA1	CV55527	SNV	splicesite	3
BRCA1	CV17695	SNV	p.Met1775Lys	3
BRCA1	CV17694	SNV	p.Met1775Arg	3

BRCA1	CV37656	SNV	p.Ile1766Ser	3
BRCA1	CV55510	SNV	p.Leu1764Pro	3
BRCA1	CV236262	Indel	splicesite	3
BRCA1	COSM35895	SNV	splicesite	3
BRCA1	CV55461	SNV	p.Gly1738Arg	3
BRCA1	CV55451	SNV	splicesite	3
BRCA1	CV37643	SNV	splicesite	3
BRCA1	CV55425	SNV	splicesite	3
BRCA1	CV55423	SNV	splicesite	3
BRCA1	CV55414	SNV	p.Ser1715Arg	3
BRCA1	CV55407	SNV	p.Ala1708Glu	3
BRCA1	CV37638	SNV	p.Gly1706Glu	3
BRCA1	CV55396	SNV	p.Arg1699Trp	3
BRCA1	CV37629	SNV	splicesite	3
BRCA1	CV37633	SNV	p.Asp1692His	3
BRCA1	CV37632	SNV	p.Asp1692Asn	3
BRCA1	CV55376	SNV	p.Asp1692Tyr	3
BRCA1	CV55365	SNV	p.Thr1685Ile	3
BRCA1	CV55364	SNV	p.Thr1685Ala	3
BRCA1	CV182165	SNV	splicesite	3
BRCA1	CV55344	SNV	splicesite	3
BRCA1	CV37620	SNV	splicesite	3
BRCA1	CV246100	SNV	splicesite	3
BRCA1	CV55342	SNV	splicesite	3
BRCA1	CV37619	SNV	splicesite	3
BRCA1	CV125722	SNV	splicesite	3
BRCA1	CV55256	SNV	splicesite	3
BRCA1	CV37604	SNV	p.Glu1559Lys	3
BRCA1	CV37605	SNV	p.Glu1559Gln	3
BRCA1	CV37598	SNV	p.Arg1495Met	3
BRCA1	CV37584	SNV	splicesite	3
BRCA1	CV55131	SNV	p.Gln1395=	3
BRCA1	CV37567	SNV	splicesite	3
BRCA1	CV37674	SNV	splicesite	3
BRCA1	COSM1559465	SNV	splicesite	3
BRCA1	CV54751	SNV	splicesite	3
BRCA1	CV37501	SNV	splicesite	3

BRCA1	CV125616	SNV	splicesite	3
BRCA1	CV37449	SNV	splicesite	3
BRCA1	CV37450	SNV	splicesite	3
BRCA1	CV54467	SNV	splicesite	3
BRCA1	CV54471	SNV	p.Arg71Lys	3
BRCA1	CV17693	SNV	p.Arg71Gly	3
BRCA1	CV54400	SNV	p.Cys64Tyr	3
BRCA1	CV17661	SNV	p.Cys61Gly	3
BRCA1	CV54199	SNV	p.Cys44Tyr	3
BRCA1	CV54191	SNV	p.Cys44Ser	3
BRCA1	CV54166	SNV	p.His41Arg	3
BRCA1	CV54152	SNV	p.Cys39Arg	3
BRCA1	CV54131	SNV	p.Thr37Lys	3
BRCA1	CV55656	SNV	p.Leu22Ser	3
BRCA1	CV55072	SNV	p.Met1Ile	3
BRCA1	CV54746	SNV	p.Met1Arg	3
BRCA1	CV54745	SNV	p.Met1Thr	3
BRCA1	CV54432	SNV	p.Met1Val	3

A function has been implemented in MATCHBOX to identify any deleterious mutations in BRCA with a Level of Evidence of code 3 or higher not listed in the table above. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1I: AZD1775, BRCA Mutations

Appendix III

Patient Drug Information Handout and Wallet Card

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **AZD1775**. 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:

AZD1775 interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are **CYP 3A4 and 2C19**. AZD1775 is broken down by CYP 3A4 and may be affected by other drugs that inhibit or induce these enzymes. AZD1775 is an inhibitor of CYP 3A4 and 2C19 and may affect the metabolism of other drugs.
- The proteins in question are **OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP.** AZD1775 is a substrate of P-gp and BCRP and may be affected by other drugs that inhibit or induce these transporters. AZD1775 is an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP and may affect transport of other drugs in and out of cells.

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

AZD1775 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:

AZD1775 must be used very carefully with other medicines that use certain **liver enzymes or transport proteins to be effective or to be cleared from your system**. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors or substrates of **CYP 3A4, 2C19, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is

_____

and he or she can be contacted at:

_____.

STUDY DRUG INFORMATION WALLET CARD	**AZD1775** interacts with **CYP 3A4, 2C19, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP**, and must be used very carefully with other medicines that interact with these enzymes and proteins.
You are enrolled on a clinical trial using the experimental study drug **AZD1775.** This clinical trial is sponsored by the NCI. **AZD1775** 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.	➢ 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 or substrates of CYP 3A4, 2C19, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP**" ➢ Before prescribing new medicines, your regular prescribers 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 _____.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1I: AZD1775, BRCA Mutations

Appendix IV

Patient Handout for Management of Diarrhea

If you develop diarrhea, call your study team. If you do not have an associated fever and/or blood or mucus in the stool, and the diarrhea is felt to be due to the study medication you are taking, your doctor may prescribe anti-diarrhea medications such as loperamide (imodium® 2 mg tablet). You should take total of 4 mg of loperamide by mouth after the first unformed stool with 2 mg every 2 hours (4 mg every 4 hours while asleep), until resolution of episode for at least 12 hours (no more than 16 mg of loperamide during a 24-hour period).

Instead of loperamide, your doctor may prescribe Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) 5 mg (2 tablets) 3 or 4 times daily (20 mg/24 hrs in divided doses is the maximum recommended dosage).

If diarrhea does not improve, or you develop additional symptoms contact your study team.