SUMMARY OF CHANGES – Protocol

For Protocol Amendment #13 to: A Phase II study of olaparib and AZD6738 in isocitrate dehydrogenase (IDH) mutant solid tumors

NCI Protocol #: 10222
Local Protocol #: 10222

NCI Version Date: April 4, 2025
Protocol Date: April 4, 2025

I. Revisions requested in CTEP Request for Amendment (RA) dated October 1, 2024:

#	Section	Comments
1.	All	Updated Version Date in Header
2.	Face Page	Updated Protocol Type and Version Date
3.	TOC	Updated Table of Contents
4.	Appendix G, Sec 5.6.3	The current EET Biobank Shipping Address replaces the former ETCTN Biorepository address
5.	Appendix G Sect 6	The current EET Biobank contact information phone number replaces that of the former ETCTN Biorepository

II. Revisions requested in CTEP Global Safety Update dated August 22, 2024:

#	Section	Comments
1.	10.3.4	Table for "Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention" updated to "Effective Date: August 30, 2024" as per NCI Memorandum dated August 22, 2024.

III. Revisions recommended in Review of Amendment #08 of Protocol #10222: "A Phase II Study of Olaparib and AZD6738 in Isocitrate Dehydrogenase (IDH) Mutant Solid Tumors" dated 05/08/2023

#	Section	Comments
1.	4.1	***Please revise the excerpt below as indicated.*** ~~Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.~~ Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all

#	Section	Comments
		individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability. RCR utilizes five person registration types. • ~~IVR~~ Investigator (IVR): MD, DO, or international equivalent, • ~~NPIVR~~ Non Physician Investigator (NPIVR): advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD), • ~~AP~~ Associate Plus (AP): clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges, • Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and • Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems. ***Please revise the excerpt below as indicated.*** An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and ~~appropriate RCR registration~~ by July 1, 2023 for all users) is required to ~~access all CTEP and~~ participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following: • Addition to a site roster, • ~~Assign~~ Selection as the treating, credit, ~~consenting,~~ or drug shipment ~~(IVR only) tasks~~ investigator or consenting person in OPEN, • ~~Act~~ Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and • ~~Assign~~ Assignment of the Clinical Investigator (CI) ~~role~~ task on the Delegation of Tasks Log (DTL). **PI Response:** All revisions made as recommended.
2.	4.2	***Please revise the excerpt below as indicated.*** In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval)

#	Section	Comments
		must meet the following criteria ~~to complete~~ for the site to be able to have an Approved status following processing of the IRB/REB approval record ~~to be completed~~: • ~~Holds~~ Have an active CTEP status, • ~~Active~~ Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster, • If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record, • Include~~s~~ the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, • List~~s~~ all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and • ~~Holds~~ Have the appropriate CTEP registration type for the protocol. ***Please revise the excerpt below as indicated.*** • Compliance with all applicable protocol-specific requirements (PSRs). **PI Response:** All revisions made as recommended.
3.	4.2.1	***Please revise the excerpt below as indicated.*** Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and ~~its~~ their associated investigators and staff on a participating roster. To view/download site registration forms: • Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users), **PI Response:** All revisions made as recommended.
4.	4.2.3	***Please revise the excerpt below as indicated.*** Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org ~~in order~~ to receive further instruction and support. **PI Response:** All revisions made as recommended.
5.	4.2.4	***Please revise the excerpt below as indicated.*** Site's registration status may be verified on the CTSU members' website.

#	Section	Comments
		PI Response: All revisions made as recommended.
6.	4.3.1	***Please revise the excerpt below as indicated.*** • A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users). ***Please revise the excerpt below as indicated.*** Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with ~~the registration system~~ patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study. **PI Response:** All revisions made as recommended.
7.	Section 5.1 and Appendix G, Section 2.1	Remove the following text from footnote 1 in the Specimen Collection Table: When completed, upload the corresponding pathology report to Rave and send a copy to the EET Biobank **PI Response:** All revisions made as recommended.
8.	5.7	Revise the Table title as follows to add text as shown: List of Biomarker Assays in Order of Priority Note for participating sites: Please see Section 5.1 for details on specimens to collect. The tissue/body fluid tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing **PI Response:** All revisions made as recommended.
9.	5.7	Update the Biomarker Table to the following. This: • **Removes the Biomarker Review Requirement in the Assay column.** • **Deletes the Use of NCI Resources column.** • **Moves the laboratory information to a new, separate column and updates this information as will eventually needed for specimen**

transfer.

Biomarker Name	Assay and CLIA: Y/N	Use (Integral, Integrated, or Exploratory) AND Purpose	Tissue/Body Fluid Tested and Timing of Assay	Mandatory or Optional	Assay Laboratory, Lab PI, and Lab PI Email
IDH1/2 mutation detection	Next-generation sequencing CLIA: Y	**Integral** To screen potential patients (eligibility criterion)	Diagnostic tissue	M	Any commercial lab
2HG plasma and tumor concentrations	LCMS/MS CLIA: N	**Integrated** To address the tumor and plasma concentration of 2HG before and after therapy	Plasma and frozen tissue specimens Tissue: Prior to initiation of treatment and after cycle 1; 5 slides archival FFPE tissue Plasma: Prior to initiation of treatment and on day 1 of cycles 2, 4 and 8 and at time of evidence of progression per study schema (plasma only; -/+ 4 days)	M[a]	Karmanos Cancer Institute, Wayne State University School of Medicine Jing Li, Ph.D. LiJing@wayne.edu

#	Section	Comments					
		WES/RNAseq	Next-generation sequencing CLIA: N	**Integrated** To confirm IDH1 and IDH2 mutations **Exploratory** To search for biomarkers of response and resistance	DNA, cDNA, and RNA from: Archival tissue or formalin-fixed tissue collected pre-treatment Formalin-fixed tissue at Week 4 DNA from blood in EDTA	M[a]	NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams, Ph.D. mickey.williams@nih.gov
		CyTOF DNA damage repair multiplex	Multiparametric flow CLIA: N	**Exploratory** To assess changes in DNA damage repair induced by olaparib/AZD6738	FFPE tissue specimens Prior to initiation of treatment and after cycle 1	M	Schalper Laboratory, Department of Pathology, Yale University School of Medicine Kurt Schalper, MD, PhD kurt.schalper@yale.edu
		Rad51	IHC CLIA: N	**Exploratory** To assess changes in DNA damage repair induced by olaparib/AZD6738	FFPE tissue specimens Prior to initiation of treatment and after cycle 1	M[a]	Center for DNA Damage and Repair, Dana-Farber Cancer Institute (DFCI) Geoffrey Shapiro, MD, PhD geoffrey_shapiro@dfci.harvard.edu

#	Section	Comments
		PI Response: All revisions made as recommended. Note that, following the 01/07/2025 Specimen Kick-off Call for Protocol# 10222 between Yale study personnel and the NCI biomarker committee, this table was further modified extensively (see changes in Section IV below).
10.	5.10.1 and 5.10.2	Please revise the second paragraph to add the NCLN Genomics Laboratory: Unstained slides will be prepared for macrodissection and nucleic acid extraction. After pathology review, macrodissection of demarcated tumor will be performed and nucleic acids will be extracted and distributed to the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) or the NCLN Genomics Laboratory for analysis. Additional tissue remaining after creating unstained slides for IHC and nucleic acid extractions will be banked for long-term storage at ambient temperature. At MoCha/NCLN Genomics Lab, the steps will be: • DNA library prepared for WES. • RNA library prepared for RNA-Seq. • Library quantitation using ddPCR for both WES and RNA-Seq • Denaturing and clustering of DNA and RNA libraries for sequencing • Sequencing of WES and RNA-Seq libraries • Data analysis for WES and RNASeq **PI Response:** All revisions made as recommended. Note that, following the 01/07/2025 Specimen Kick-off Call for Protocol# 10222 between Yale study personnel and the NCI biomarker committee, reference to the NCLN Genomics laboratory were removed.
11.	5.10.1.4	Revise the site performing the correlative study for WES to add the NCLN Genomics Laboratory: 5.10.1.4 Site Performing Correlative Study NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Dr. P. "Mickey" Williams, Ph.D. **PI Response:** All revisions made as recommended. Note that, following the 01/07/2025 Specimen Kick-off Call for Protocol# 10222 between Yale study personnel and the NCI biomarker committee, reference to the NCLN Genomics laboratory were removed.
12.	5.10.2.4	Revise the site performing the correlative study for RNAseq to add the NCLN Genomics Laboratory:

#	Section	Comments
		5.10.2.4 Site Performing Correlative Study NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Dr. P. "Mickey" Williams, Ph.D. **PI Response:** All revisions made as recommended. Note that, following the 01/07/2025 Specimen Kick-off Call for Protocol# 10222 between Yale study personnel and the NCI biomarker committee, the assay contact was changed to Chris Karlovich instead of Mickey Williams and reference to the NCLN Genomics laboratory were removed.
13.	10.3.3	***Please verify if 10222 uses Rave CTEP-AERS Integration, and include this subsection as needed.*** **1.1.1 Rave-CTEP-AERS Integration** The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AEs) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave. ***Include the following (highlighted) paragraphs about pre-treatment AEs only if the study requires reporting of pre-treatment AEs and the CTSU standard Pre-Treatment AE form is used. Pre-existing medical conditions are not considered adverse events and therefore should not be reported on the Pre-Treatment Adverse Event form.*** Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form. Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened condition should be reported in Rave as a routine AE. Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational agent/intervention are collected using the Late Adverse

#	Section	Comments
		Event form. Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave: • The reporting period (course/cycle) is correct, and • AEs are recorded and complete (no missing fields) and the form is query free. The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation. Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS. In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave. Additional information about the CTEP-AERS integration is available on the CTSU members' website: • Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*, and • Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*. NCI requirements for SAE reporting are available on the CTEP website: • NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf. **PI Response:** All revisions made as recommended regarding Rave CTEP-AERS Integration. In an email dated 1/6/2025, Theradex confirmed that the CTSU standard pre-treatment form is not in Rave for Theradex studies, including this one. Therefore,

#	Section	Comments
		the relevant language above has not been added.
14.	13.2	***Please revise the excerpt below as indicated.*** Medidata Rave is ~~a~~ the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. Requirements to access Rave via iMedidata: • A valid ~~account, and~~ CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users), and • Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements: o Rave CRA or Rave CRA (Lab Admin) role~~,~~ must have a minimum of an Associate Plus (AP) registration type, o Rave Investigator role~~,~~ must be registered as a~~n~~ Non-Physician Investigator (NPIVR) or Investigator (IVR), and o Rave Read Only or Rave SLA role~~, site staff~~ must have at a minimum an Associate~~s~~ (A) registration type. ***Please revise the excerpt below as indicated.*** Upon initial site registration approval for the study in the Regulatory ~~Support System (RSS)~~ application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. ***Please revise the excerpt below as indicated.*** Site staff ~~that~~ who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in ~~RSS~~ the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section ~~at www.ctsu.org/RAVE/~~ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response:** All revisions made as recommended.
15.	13.3	***Please verify if 10222 utilizes the Data Quality Portal, and add the following subsection as appropriate.***

#	Section	Comments
		1.2 Data Quality Portal The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules. CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website. To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules. ***Include the following paragraph only if study is not using the Calendaring functionality in Rave; otherwise, delete.*** This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count. **PI Response:** All revisions made as recommended.
16.	Appendix G	Under testing and storage facilitates, up the entry for MoCha to the following: RNA and DNA sequencing: P. "Mickey" Williams, Ph.D. NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR)

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td><u>PI Response:</u>
All revisions made as recommended. Note that, following the 01/07/2025 Specimen Kick-off Call for Protocol# 10222 between Yale study personnel and the NCI biomarker committee, the contact was changed to Chris Karlovich instead of Mickey Williams and reference to the NCLN Genomics laboratory were removed.</td></tr>
<tr><td>17.</td><td>Appendix G, Section 3</td><td>Update the Table below to add the NCLN Genomics Laboratory to the MoCha entry:
<table>
<tr><th>Testing Facility</th><th>Platform</th><th>Biomarker/Correlative</th></tr>
<tr><td>Li Lab, Karmanos</td><td>LC-MS/MS</td><td>Determination of 2-HG in tissue and plasma</td></tr>
<tr><td>NCLN Genomics Laboratory or MoCha, Frederick National
Laboratory for Cancer Research (FNLCR)</td><td>Illumina-based next-generation sequencing</td><td>DNA whole exome sequencing and RNA transcriptomic sequencing</td></tr>
<tr><td>Schalper Lab, Yale</td><td>QIF/CyTOF-IMC</td><td>In situ analysis of tumor DNA repair markers</td></tr>
<tr><td>Shapiro Lab, Dana-Farber</td><td>Immunohistochemistry</td><td>Detection of Geminin and RAD51</td></tr>
</table>
<u>PI Response:</u>
All revisions made as recommended. Note that, following the 01/07/2025 Specimen Kick-off Call for Protocol# 10222 between Yale study personnel and the NCI biomarker committee, this table was further modified to remove reference to the NCLN Genomics Laboratory.</td></tr>
<tr><td>18.</td><td>Appendix G Sec 5.1.1</td><td>Revise the URL for the EET Biobank Kit Management System as below:
Kits for the collection and shipment of specimens to the EET Biobank can be ordered online via the Kit Management system: https://kits.bpc-apps.nchri.org/.
<u>PI Response:</u>
All revisions made as recommended.</td></tr>
<tr><td>19.</td><td>Appendix G, Section 5.2.1</td><td>Revise the third sentence in the third paragraph as follows:
For newly acquired biopsies without a corresponding pathology report, the</td></tr>
</table>

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>radiology and operative report(s) must also be uploaded into Rave, when available.

<u>PI Response:</u>

All revisions made as recommended.</td></tr>
<tr><td>20.</td><td>Appendix G, Section 5.2.3.2</td><td>For Step 2, revise the last final sentence of the last bullet as follows.

Do not redact SPID, block number, diagnosis or relevant dates (such as collection date) and include the UPID and patient study ID on each document (either by adding a label or hand writing).

<u>PI Response:</u>

All revisions made as recommended.</td></tr>
<tr><td>21.</td><td>Appendix G, Section 5.6</td><td>In the second paragraph in Section 5.6, replace “surgical” with “operative”.

Insert the following text as new Section 5.6.1. Renumber current Section 5.6.1 Specimen Shipping Instructions as 5.6.2.

5.6.1 Required Forms for Specimen Submissions

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.
<table>
<tr><th>Tissue</th><th>Required Forms</th></tr>
<tr><td>Archival</td><td>1. Shipping List
2. Corresponding Pathology Report</td></tr>
<tr><td>New Biopsy</td><td>1. Shipping List
2. Tissue Biopsy Verification Form (Appendix G, Section 8)
3. Diagnostic Pathology Report
4. Operative and/or Radiology Report</td></tr>
<tr><td>Blood</td><td>1. Shipping List</td></tr>
</table>
<u>PI Response:</u>

All revisions made as recommended.</td></tr>
<tr><td>22.</td><td>Appendix G, Section 5.6.2.1</td><td>In the fifth sentence, replace surgical with operative.

Place the specimen(s) and a copy of the shipping manifest and corresponding reports such as operative or radiology reports into the insulated shipping container.</td></tr>
</table>

#	Section	Comments
		PI Response: All revisions made as recommended.

IV. Revisions following NCI#10222 Specimen Kick-Off Call with NCI held on Tuesday, January 7, 2025

#	Section	Comments
1.	5.1	Reference to NCLN Genomics laboratory removed
2.	5.7	Prioritization for use of tumor tissue specimens modified
3.	5.7	Figure 7 modified to reflect changes to biomarker plan. Note added that 2-HG assay will use remaining FFPE tissue that was sent to the EET Biobank
4.	5.7	Table "List of Biomarker Assays in Order of Priority" rewritten to reflect changes to biomarker plan and assay performance locations
5.	5.9.1.1	Note was added that no archival or frozen tissue specimens were received at the Li Laboratory as of April 2025. Instead, as of Amendment 13 (version April 4, 2025) of this protocol, this assay will use FFPE tissue collected at pre-treatment and on treatment cycle 1 remaining at EET Biobank following completion of the higher priority assays.
6.	5.10.3	Section modified to add IF to look at gamma-H2AX and RAD51 and update biomarkers
7.	Appendix G	Contact for RNA/DNA sequencing changed to Chris Karlovich
8.	Appendix G, Section 2	Figure modified to reflect changes to biomarker plan. Note added that 2-HG assay will use remaining FFPE tissue that was sent to the EET Biobank
9.	Appendix G, Section 2.1	Prioritization for use of tumor tissue specimens modified
10.	Appendix G, Section 3	MoCha lab detail added and clarification for mQIF and CyTOF-IMC assays
11.	Appendix G, Section 6	Study PI changed from Navid Hafez to Patricia LoRusso. Contact information updated
12.	Appendix G, Section 6	EET biobank phone number updated
13.	Appendix G, Section 6	Contact information for DNA and RNA sequencing added

V. Additional revisions required by CTEP

#	Section	Comments
1.	Face Page	Removed EDDOP from list of participating Organizations
2.	3.3	Word 'genders' replaced with 'sexes' to comply with 2025 Executive Order regarding Defending Women

VI. Revisions made in response to CTEP review of Amendment 11 dated 03/21/2025

a. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	10.3.4	I noticed that the Table for "Expedited Reporting Requirements for NCI IND/IDE Agents" mistakenly included in the protocol is for Phase 1 and Early Phase 2 Studies. Please update the Table for "Expedited Reporting Requirements for NCI IND/IDE Agents" for **Late Phase 2 and Phase 3 Studies** as per NCI Guidelines for Investigators, effective August 30, 2024. **PI Response:** The Table has been updated as requested.

b. Company Comments – Requiring a Response:

#	Section	Comments
2.	10.1.1.2	Identified Risks for Ceralasertib – MDS/AML is not specifically documented for Cera **PI Response:** CAEPR for AZD6738 (ceralasertib, NSC 802785) has been updated to Version 2.1 (February 27, 2025) in response to CTEP Request for Rapid Amendment (RRA) dated April 3, 2025 and now references leukemia secondary to oncology chemotherapy and Myelodysplastic syndrome
3.	N/A	MDS/AML is considered an AESI for Ceralasertib, but this is not identified in the protocol - this appears in Section 10.8 for Olaparib **PI Response:** As adding MDS/AML as an Adverse Event of Special Interest (AESI) requires NCI approval, an inquiry was made to CTEP regarding this comment and a response received 03/26/25: *In terms of listing AML/MDS as an AESI, that can probably be updated in the information at annual review.* Therefore, no changes have been made at this time.
4.	7.3	• **MDS/AML** is considered an identified risk (ADR) for olaparib and potential risk for ceralasertib. Both products incorporate the following guidance in their respect TMG/dose modification guidelines, recommend the site incorporate the same (or similar) **Management of prolonged haematological toxicities**

#	Section	Comments
		Participant should be referred to a haematologist for further investigations and management in the event of prolonged haematological toxicity such as: • ≥ 2week interruption/delay in study intervention due to CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence • ≥ 2week interruption/delay in study intervention due to CTCAE Grade 3 or worse neutropenia (ANC < 1×10^9/L) ≥ 2week interruption/delay in study intervention due to CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50×10^9/L) Consider checking weekly differential blood counts including reticulocytes and peripheral blood smear. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study intervention should be discontinued if blood counts do not recover to CTC Grade 1 or better within 4 weeks of dose interruption. Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Study intervention should be discontinued if participant's diagnosis of MDS and/or AML is confirmed. **PI Response:** This information has been added to Section 7.3 as recommended.

VII. Revisions requested in CTEP Request for Rapid Amendment (RRA) dated April 3, 2025:

#	Section	Comments

1.	10.1.1.2	CAEPR for AZD6738 (ceralasertib, NSC 802785) updated to Version 2.1 (February 27, 2025):
		• Added New Risk:
		  • Less Likely: Headache
		  • Rare but Serious: Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome
		  • Also Reported on AZD6738 Trials But With Insufficient Evidence for Attribution: Acute kidney injury; Ascites; Chest pain - cardiac; Disease progression; Dysphagia; Electrocardiogram QT corrected interval prolonged; Heart failure; Hepatitis viral; Hepatobiliary disorders - Other

#	Section	Comments

		(biliary obstruction); Hepatobiliary disorders - Other (cholangitis); Hypokalemia; Pericardial effusion; Pulmonary edema; Renal and urinary disorders - Other (acute renal insufficiency); Respiratory failure; Sepsis; Stroke; Superior vena cava syndrome; Thromboembolic event; Vascular disorders - Other (thrombophlebitis)
		
		• Increase in Risk Attribution:
		  • Changed to Likely from Less Likely: Vomiting
		  • Changed to Less Likely from Also Reported on AZD6738 Trials But With Insufficient Evidence for Attribution: Edema limbs; Infections and infestations - Other (COVID-19); Lung infection; Weight loss
		
		• Decrease in Risk Attribution:
		  • Changed to Also Reported on AZD6738 Trials But With Insufficient Evidence for Attribution from Less Likely: Aspartate aminotransferase increased; Dizziness; Pain
		
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
		  • Added: Diarrhea; Vomiting
		
		• Provided Further Clarification:
		  • Gastrointestinal disorders - Other (gastroenteritis) (under Also Reported on AZD6738 Trials But With Insufficient Evidence for Attribution) is now reported as Infections and infestations - Other (gastroenteritis) (under Also Reported on AZD6738 Trials But With Insufficient Evidence for Attribution)

NCI Protocol #: 10222

Local Protocol #: 2000027026

ClinicalTrials.gov Identifier: NCT03878095

TITLE: A Phase II study of olaparib and AZD6738 in isocitrate dehydrogenase (IDH) mutant solid tumors

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NCI-Supplied Agent(s): *Olaparib[NSC# 747856]; AZD6738 [NSC #802785]*

IND #: [redacted]
IND Sponsor: *DCTD, NCI*

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SCHEMA

Synopsis:
This is a phase II, open-label study of PARP inhibition (olaparib) and ATR inhibition (AZD6738) in subjects with recurrent/progressive, IDH1/2-mutant solid tumors.

Objectives:
Primary:

1. To determine the **overall response rates** of olaparib and AZD6738 in subjects with recurrent/progressive IDH1/2-mutant solid malignant tumors, who will be recruited to 2 cohorts:
    a. Cholangiocarcinoma (this cohort has closed to accrual)
    b. Other solid malignant tumors.

Secondary:

1. To assess the **progression free survival** (PFS) of olaparib and AZD6738 in adults with recurrent/progressive IDH1/2-mutant solid malignant tumors.
2. To estimate the **overall survival** (OS) in adults with recurrent/progressive IDH1/2-mutant solid malignant tumors.
3. To assess the **duration of response** in adults with recurrent/progressive IDH1/2-mutant solid malignant tumors.
4. To assess the **safety and tolerability** of the combination of olaparib and AZD6738

Exploratory:

1. To evaluate 2HG concentration in plasma by mass spectrometry and correlate with treatment response, prior to beginning treatment and on day 1 of cycles 2, 4 and 8 of therapy and at time of confirmed evidence of progression.
2. To evaluate 2HG levels in tumor biopsies prior to the beginning of treatment and while on therapy and correlate with treatment response.
3. Correlate 2HG concentration in plasma and in tumor biopsies.
4. To evaluate DNA double strand breaks (DSBs) as measured by CyTOF-IMC in tumor biopsies before and after treatment with olaparib and AZD6738.

An overall treatment schema is shown below in Figure 1. This is a phase II two-arm, open-label study of PARP inhibition (olaparib) and ATR inhibition (AZ6738) in subjects with recurrent/progressive, IDH1/2-mutant solid tumors. An overall treatment schema is shown below. Patients will be treated with olaparib 300 mg q12hrs each day of a 28-day cycle in tablet formation and AZD6738 160 mg qday on days 1-7 of a 28-day cycle in tablet formation until disease progression, unacceptable toxicity, withdrawal of consent or death. Tablet formation of olaparib is preferred over capsule formulation based on recent work demonstrating equivalent efficacy with a reduced pill burden (Mateo, Target Oncol, 2016).

Patients with IDH1/2 mutations previously identified in a CLIA-certified laboratory are eligible for the trial. Whole exome sequencing and RNA sequencing will be performed prior to study

completion for the purpose of data analysis. This analysis will be performed on pre-treatment biopsy tissue (see next paragraph) or archival formalin-fixed paraffin embedded (FFPE) specimens, if the former is not available and archival tissue is available.

Patients will undergo a pre-treatment biopsy within 2 weeks of starting therapy. Repeat biopsy will be required 4 weeks from the start of treatment. The biopsy will consist of at least 6 passes of a large gauge needle (such as 16 or 18g) for core biopsy. Patients in these cohorts must have tumors determined to be easily accessible for biopsy. Tumor biopsies will be performed on the most accessible biopsable site of disease. All possible precautions to avoid complications will be taken, including discussions in multidisciplinary meetings, if needed.

Correlative studies will include determination of 2HG levels in archival FFPE specimens and biopsy frozen tissue. This will be done using LC-MS/MS, which will be performed in the Karmanos Cancer Institute Pharmacology Core. Blood samples for 2-HG analysis will be collected prior to starting therapy and on day 1 of cycles 2, 4, and 8 of therapy and at time of confirmed evidence of progression. A window of +/- 4 days for each intervention is permitted.

All eligible patients will be imaged within 30 days prior to starting therapy, and then after every two cycles of therapy (8 weeks) for the first twelve months, or until time of progression, unacceptable toxicity, withdrawal of consent, death, or any other discontinuation criteria, whichever occurs first. If partial response (PR) or complete response (CR) is documented, a confirmatory scan will be performed 4 weeks later for PR/CR (whichever occurs first). After 12 months, patients will undergo tumor assessments every 12 weeks until confirmed disease progression.

Patients will be imaged with CT and/or MRI scans of the chest, abdomen and pelvis. Patients who start a new anti-cancer therapy in the absence of disease progression should continue to follow the protocol schedule until there is confirmed disease progression, withdrawal of consent, death, or any other discontinuation criteria, whichever occurs first.

Although pre- and post-treatment biopsies will be critical to evaluating treatment response with respect to 2-HG analysis, we understand that it is not always possible to obtain fresh biopsy tissue. For example, a patient may have measurable disease that is not easily accessible for core needle biopsy. Thus we will practice an opt-out policy, wherein a patient may opt out of pre- and on-treatment biopsies if biopsy is not possible or the patient does not consent to biopsy **and** permission of the study PI is obtained. For all patients, archival formalin-fixed paraffin embedded (FFPE) specimens will be used, if possible, for baseline LC-MS measurement of 2HG levels in tumor. If a patient opts out of pre- and on-treatment biopsies, that patient must have an adequate archival specimen to enroll on the trial. Ten of the 14 patients in each arm of the first stage of this Simon two-stage study must consent to biopsies. Thus if 4 patients in an arm have already opted out, further patients may only enroll on that arm (in the first stage) if they agree to undergo the pre- and on-treatment biopsies.

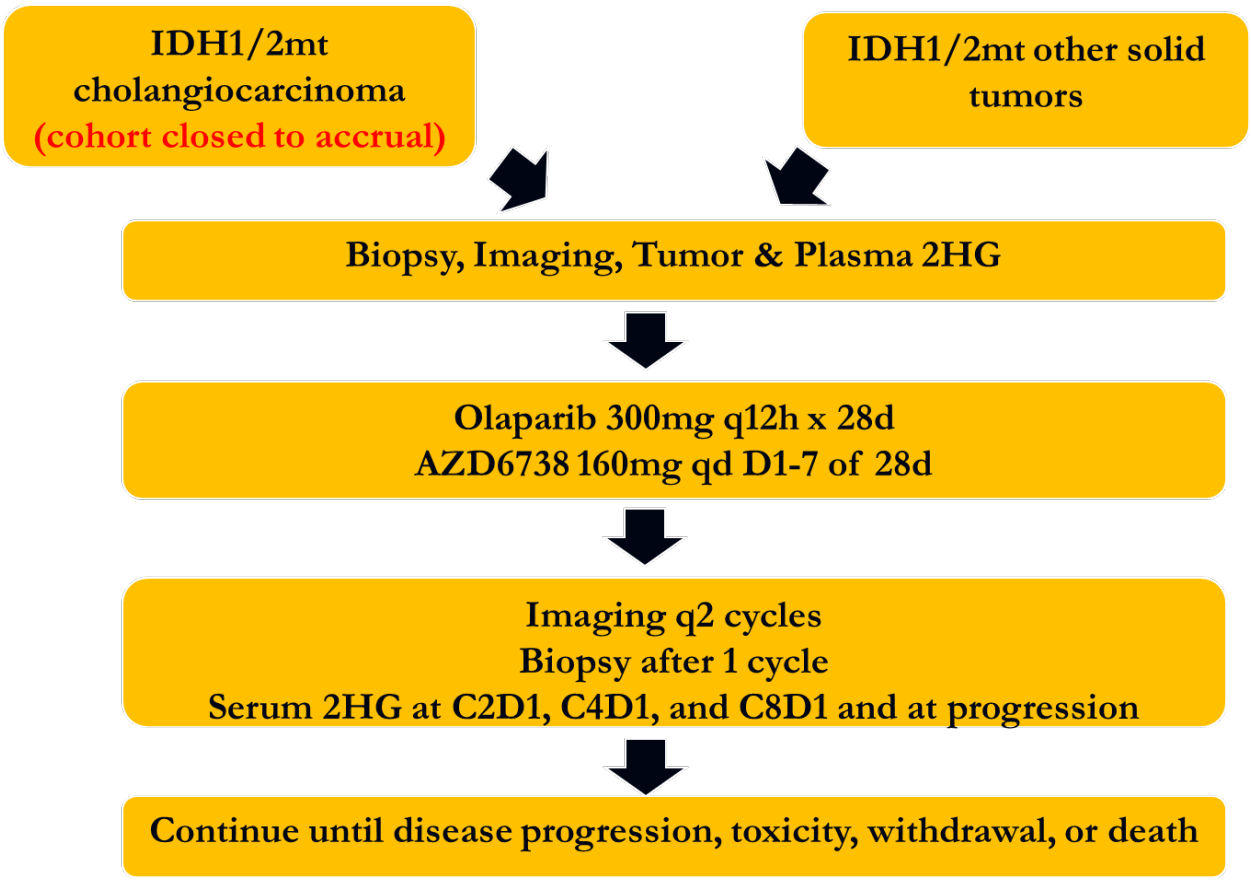
In order to maximize the availability of newly obtained specimens for 2-HG analysis, at least 10 biopsies will be required in each group (cholangiocarcinoma and other solid tumors) of 14 patients treated in the first stage of this Simon two-stage design. Patients will not be “replaced.”

For example if 13 patients have been enrolled and 9 have agreed to biopsies, the 14th patient enrolled on that arm must be one who agrees to a biopsy. However if that patient consents to the trial and withdraws consent for biopsies, that patient will continue participation on the trial.

We expect to enroll between 28 and 50 patients on this trial.

Figure 1. Study schema

Study schema



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1. OBJECTIVES

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    b. Other solid malignant tumors.

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4. To evaluate DNA double strand breaks (DSBs) as measured by CyTOF-IMC in tumor biopsies before and after treatment with olaparib and AZD673.

2. BACKGROUND

2.1 IDH mutant solid tumors

Mutations in isocitrate dehydrogenase (IDH) enzymes are most common in low grade tumors of the central nervous system, occurring in over 70% of secondary glioblastoma multiforme (GBM) and low grade gliomas. In these instances, IDH mutations conferred improved overall survival (OS) in patients with anaplastic astrocytomas and secondary GBM. However, the prognosis remains poor in the latter, with an average survival of 14.6 months.[1] IDH1/2 mutations have also been identified in 10-23% of patients with intrahepatic cholangiocarcinomas,[2–4] with unclear effects on OS.[2,3] Intrahepatic cholangiocarcinoma (IHCC), which represents about 20-30% of all cases of cholangiocarcinoma, is often found in patients with cirrhosis. Only 30-40% of IHCC patients have resectable disease at the time of diagnosis and survival rates are dismal, with 25% of patients alive at one year, and 5% alive at five years after diagnosis.[5] The standard of care for advanced IHCC is chemotherapy with cisplatin and gemcitabine, which has a median overall

survival (OS) of 11.7 months compared to 8.1 months with gemcitabine alone.[6] However, poor liver function and low performance status, as well as advanced age often limit the use of combination chemotherapy for patients with IHCC.[5] Among 203 patients with unresectable IHCC who did not opt for any therapy, the median survival was 3.0 months.[7] There is no standard second-line therapy for advanced IHCC, making it imperative to explore alternate therapeutic approaches to this challenging disease. Finally, a low frequency (<5%) of IDH1/2 mutations has been described in other solid tumors, including primary glioblastoma, colorectal cancer, esophageal cancer, bladder cancer, melanoma, prostate carcinoma, and breast adenocarcinoma.[8,9] In summary, IDH1/2 mutations are found most frequently in a number of cancers with poor baseline prognoses, and may in fact confer additional risk. Establishing new therapeutic options for patients whose tumors harbor such mutations is thus a priority.

2.2 Rationale

2.2.1 Introduction

2-Hydroxyglutarate (2HG) exists as two enantiomers, (R)-2HG and (S)-2HG, and both are implicated in tumor progression via their inhibitory effects on α-ketoglutarate (αKG)-dependent dioxygenases. The former is an oncometabolite that is induced by the neomorphic activity conferred by isocitrate dehydrogenase-1 and -2 (IDH1/2) mutations, while the latter is produced under pathologic processes such as hypoxia. Our collaborators in the Bindra and Glazer laboratories recently made the novel discovery that IDH1/2 mutations induce a defect in homologous recombination repair (HRR) which renders tumor cells exquisitely sensitive to Poly (ADP-Ribose) polymerase (PARP) inhibitors.[10] Remarkably, this phenotype can be completely reversed by treatment with small molecule inhibitors of mutant IDH1, and it can be entirely recapitulated by treatment with 2HG alone in cells with WT IDH1/2.

Our collaborators performed a comprehensive series of studies to test whether it was possible to detect mutant IDH1/2-dependent synergistic, synthetic lethal interactions using a variety of DNA repair inhibitors, demonstrating IDH1-dependent PARP and ATR inhibitor sensitivity in a range of clinically relevant models *in vitro* and PARP inhibitor growth restriction *in vivo*. These studies also revealed a marked interaction between PARP inhibitors and ATR inhibitors in IDH1-mutant cells. **These data indicate that it is possible to induce highly effective levels of tumor cell kill without a DNA damaging agent.** In parallel, another laboratory independently reported a similar synthetic lethal interaction between IDH1/2 mutations and PARP inhibitors.. Collectively, these findings directly challenge the current therapeutic strategy to block IDH-mutant function, and they instead provide a novel approach to treat these tumors with PARP inhibitors. Furthermore, these results uncover an unexpected link between oncometabolites, altered DNA repair, and genetic instability.

This trial directly translates our collaborators' recent findings into a biomarker-driven clinical trial. **We will test the efficacy of olaparib combined with the ATR inhibitor, AZD6738, using the recommended Phase II dosing regimen that was recently established by AstraZeneca.** This study will focus on IDH1/2-mutant solid tumors, and

it will utilize a Simon 2-stage design.

Previous data suggest that patients enrolled will most likely be affected by cholangiocarcinoma, for which there are very limited treatment options and thus there is a great unmet need. In addition to these patients, we will include a second group of patients who have tumors with IDH1/2 mutations in other tissue types. Multiple unique biomarkers will be employed in this trial, including 2HG detection by LC/MS in plasma and tumor biopsies and determination of γH2AX foci and other markers of DNA double strand breaks (DSBs) by CyTOF in tumor biopsies.

These studies have the potential to establish a completely novel treatment approach for IDH1/2-mutant tumors, and they will lay the groundwork for future studies aimed at **exploiting, rather than suppressing, 2HG-induced BRCAness** in a wide range of solid tumors.

2.2.2 Background

The normal function of isocitrate dehydrogenase (IDH) enzymes is to catalyze the conversion of isocitrate to α-ketoglutarate (αKG) in the citric acid cycle. Recurring IDH1 mutations were identified in two independent cancer genome sequencing projects focused on gliomas and acute myeloid leukemia (AML).[11,12] Subsequent studies revealed that IDH1 mutations occur in more than 70% of low grade gliomas and up to 20% of higher grade tumors (e.g., secondary glioblastoma multiforme; GBM) and 10-23% of patients with intrahepatic cholangiocarcinomas.[2–4] Additionally, mutations were also identified in IDH2, the mitochondrial homolog of IDH1, in about 4% of gliomas and 10% of AMLs.[1,8] Mutations in IDH1/2 also occur in a small percentage (<5%) of other solid tumors, including colorectal cancer, esophageal cancer, bladder cancer, melanoma, prostate carcinoma, breast adenocarcinoma.[8,9]

Nearly all known IDH1/2 alterations are heterozygous missense mutations that confer a neomorphic activity on the encoded enzymes, such that they convert α-KG to (R)-2HG (Figure 2).[13] Emerging research indicates that (R)-2HG is an oncometabolite which exerts its effect via altering chromatin methylation, possibly by competitive inhibition of α-KG-dependent tumor suppressor enzymes.[14] Another hypothesized mechanism is the induction of mitochondrial dysfunction and inability to manage oxidative stress.[15] (R)-2HG appears to exert its regulatory effects via the inhibition of αKG-dependent dioxygenases.[14]

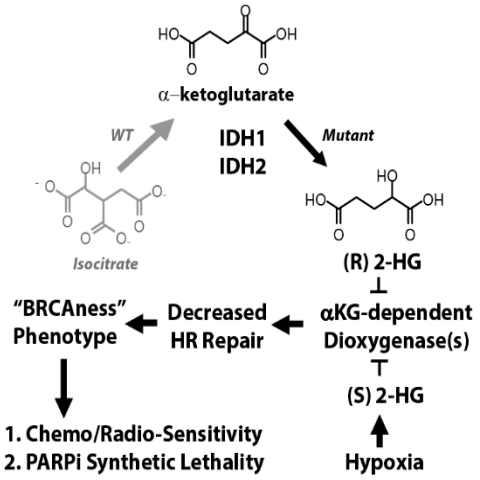


Fig. 2. Proposed mechanism of action of mutant IDH1/2-induced BRCAness and consequent PARP inhibitor synthetic lethality.

2.2.3 IDH1/2 mutated solid tumors induce a defect in homologous recombination repair

In work recently published in *Science Translational Medicine*, our collaborators discovered that **IDH1/2 mutations induce a defect in homologous recombination repair that renders tumor cells sensitive to inhibition of poly (ADP-ribose) polymerase (PARP) and ataxia-telangiectasia mutated and Rad3 related (ATR) gene products**.[10] When 2HG accumulates in IDH1-mutant cells, HRR is disrupted, causing cells to rely on alternative, low fidelity DNA repair pathways, thus hastening genomic instability and cell death. This phenotype renders them increasingly susceptible to agents that impair the DNA damage response, such as inhibitors of PARP and ATR.

Multiple aspects of the IDH1/2-induced "BRCAness" phenotype were demonstrated in a range of clinically relevant models *in vitro*, including patient-derived glioma cell lines and primary AML bone marrow cultures. For example, our collaborators tested a collection of early-passage, patient-derived IDH1-WT and -mutant glioma cell lines available at our institution. IDH1 mutations were confirmed by sequencing as reported previously,[16] and they also confirmed that it was possible to detect 2HG production in samples harboring an IDH1 R132H or R132C mutation. They detected increased baseline persistence of DSBs by comet assay in the primary glioma cell lines harboring IDH1 mutations, which is a classic approach to assess functional DSB repair activity.[17]

The HRR defect could be recapitulated in matched WT cells exposed to exogenous 2HG and was dose-dependent. Our collaborators detected PARP inhibitor sensitivity in the IDH1- mutant primary glioma cultures compared to two IDH1-WT cultures by clonogenic survival, and found that 2HG exposure could recapitulate PARP inhibitor sensitivity in WT cultures. Importantly, these data confirm that the IDH1-associated HRR defect can be detected in grades 2, 3, and 4 glioma. Mechanistically, this phenotype can be entirely recapitulated by exposure to either 2HG enantiomers, and it cannot be explained by the alterations in NAD+ levels that have been seen in IDH1/2-mutant cancers.[18] In addition, they found that 2HG exposure induced elevated rates of DSBs in a range of cell lines with diverse genetic backgrounds, including immortalized astrocytes, primary melanoma cultures, breast cancer cell lines, and U2OS cells, suggesting that this is a fundamental effect of this oncometabolite.

These data support our rationale to test IDH1/2-mutant tumors beyond gliomas. Recent data from the Gunel laboratory at Yale University showed that IDH1 mutations in gliomas that are initially present at diagnosis appear to persist after recurrence.[16] Similarly, persistence of the IDH1 mutation has also been found in relapsed AMLs that harbored the mutation at initial diagnosis.[19] Thus, we expect that there will be persistent 2HG production and subsequent HR deficiency in recurrent IDH1/2-mutant tumors, making this group a suitable population for our study.

2HG-induced HR suppression appears to be mediated via direct inhibition of αKG-dependent dioxygenases, in particular KDM4A. Our collaborators recapitulated the IDH1/2-associated HR-defective phenotype by treatment of WT cells with small molecule KDM4A inhibitors, and could reverse it in mutant cells by overexpression of

KDM4A. Importantly, they found that treatment with a mutant IDH1-specific small molecule inhibitor known to potently suppress 2HG production reversed the observed HR defect and eliminated the associated PARP inhibitor sensitivity. They demonstrated this reversal in both mutant IDH1/2 cell lines, and in a cell line harboring an endogenous IDH1 mutation. Reversal of the mutant IDH1-associated DSB repair defect was confirmed using three unique small molecule inhibitors of the mutant protein, and with siRNAs targeting the IDH1 gene, thus ruling out potential off-target effects of the inhibitors.

Our collaborators sought to harness the inherent HR deficiency in IDH1/2 mutant cells by targeting these specific mechanisms of DNA damage repair to achieve synthetic lethality. A focused, unbiased screen of their R132H IDH1 mutant HeLa cell line with a library of DNA damaging agents and DNA repair inhibitors revealed an unexpected sensitivity of IDH1 mutant cells to PARP (an enzyme critical to the repair of DNA single-strand breaks via base excision repair)[20] or ATR (an enzyme recruited to stalled replication forks which enables the halting of the cell cycle via phosphorylation of CHK1 while replication forks are stabilized).[21] Inhibition of either enzyme resulted in the accumulation of DNA double strand breaks as measured by γH2AX and 53BP1 foci.

2.2.4 IDH1/2 mutated solid tumors are sensitive to inhibition with PARP and ATR inhibitors

Our colleagues in the laboratory of Ranjit Bindra explored the HRR deficiency of IDH1/2 mutated solid tumors with a comprehensive cytotoxicity screen of our R132H IDH1 mutant HeLa cell line with a large collection of DNA damaging agents and DNA repair inhibitors. This revealed an unexpected sensitivity of IDH1 mutant cells to inhibition of both PARP and ATR (Figure 3). Sensitivities to PARP inhibitors were profound, and approached a 50-fold difference compared to IDH1-wildtype (WT) cells with the FDA-approved PARP inhibitor, olaparib. They then demonstrated this PARP sensitivity across five unique and genetically diverse cell line pairs that were engineered to express either the wild-type (WT) or the mutant IDH1/2 proteins and confirmed the observed DSB repair defect using multiple orthogonal functional assays. This interaction was demonstrated in several pre-clinical models, including IDH1/2-mutant primary patient-derived cell lines and genetically-matched tumor xenografts. Suppression of HR by 2HG was significant and was observed after the attenuation of two key HR genes, BRCA2 and Rad51, using the well-established DR-GFP assay to measure the activity of this pathway.

Summary of initial sensitivity screen

Small-molecule inhibitor		IC_{50} (μM)		WT/Mut ratio
Name	Target(s)	IDH1WT	IDH1Mut	
BMN-673	PARP	0.27	0.03	9.0
VE-822	ATR	0.16	0.06	2.6
TH287	MTH1	0.73	0.75	1.0
TCS2312	CHK1	0.23	0.22	1.0
BEZ-235	PI3K/mTOR	0.07	0.06	1.3
KU55933	ATM	8.65	6.01	1.4
AZD7762	CHK1	0.08	0.07	1.2
NU-7441	DNA-PK	6.03	6.71	0.9
KU0060648	DNA-PK	0.03	0.03	1.0
MK1775	Wee1	0.27	0.21	1.3

Figure 3.

IDH1 mutant mouse xenografts treated with olaparib showed a statistically significant growth delay when compared to vehicle control. In contrast, no statistically significant differences were detected between olaparib and vehicle in IDH1-WT tumor xenografts (Figure 4). Given their recent screen demonstrating sensitivity of IDH1 mutated cells to ATR inhibition, our collaborators sought to test whether a combination of PARP and

ATR inhibitors would be synergistic. Using Combenefit, an open-access software tool that enables the visualization, analysis and quantification of drug combination effects,[22] they confirmed a marked, synergistic interaction between PARP and ATR inhibitors, which was most dramatic in IDH1-mutant cells (Figure 5).

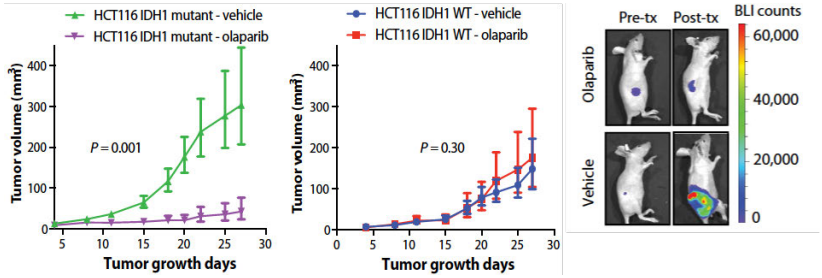


Figure 4. (Left) PARP inhibitors selectively kill HCT116 IDH1-mutant tumor xenografts with (Middle) minimal effects on IDH-WT xenografts; (Right) BLI monitoring of treatment responses

Based on these findings, we have designed a Phase II clinical trial using the FDA-approved PARP inhibitor olaparib and AZD6738, an ATR inhibitor, for patients with IDH1/2 mutated advanced solid tumors that have progressed despite standard therapy (Figure 6).

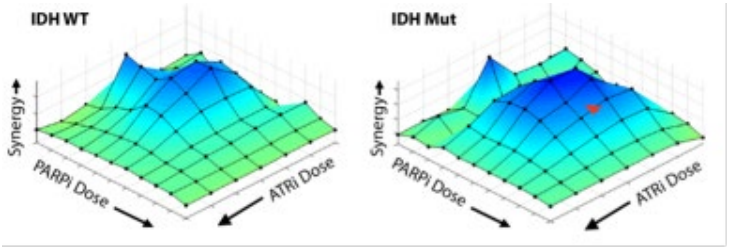


Figure 5. Example of synergy with regard to tumor cell viability between representative PARP and ATR inhibitors (BMN-673 and VE-822, respectively) which is enhanced in IDH-mutant

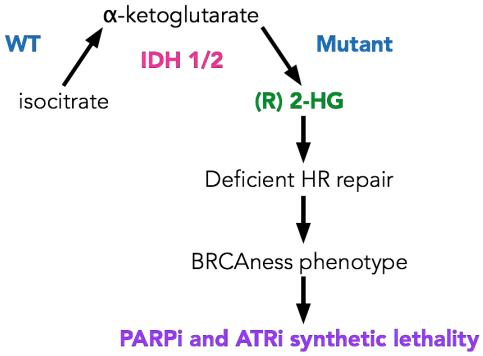


Figure 6. Conceptual schema

2.3 CTEP Agents

2.3.1 Olaparib

Investigators should be familiar with the current olaparib (AZD2281) Investigator's Brochure.

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to

the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo[23,24] and in the clinic.[25] The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair.[26,27] Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

Olaparib was first reported as an inhibitor of PARP1/2 in 2008.[28] The phase I study of olaparib, reported in 2009, initially enrolled 60 patients with a variety of advanced solid tumors, with a population enriched for carriers of *BRCA1/2* mutations.[29] Twenty-two participants had such a mutation and one more declined testing but was deemed a likely carrier due to family history. Responses were seen only in this subset of patients, of whom 47% responded by RECIST criteria and 63% had either stable disease or a response. Demonstrating proof of mechanism, the investigators used immunoblotting of post-treatment biopsies to prove that among patients who responded, PARP was effectively inhibited. Moreover, they found that γH2AX foci, a marker of DSBs, increased only six hours after treatment in plucked eyebrow hair follicles, proving that olaparib-mediated PARP inhibition results in the formation of unrepaired DSBs. Toxicities primarily included fatigue, nausea, and vomiting. An expansion cohort of 48 patients with ovarian cancer and germline *BRCA1/2* mutations again demonstrated the potential of PARP inhibition in *BRCA* mutated cancers, with an objective response rate (ORR) of 40%.[30] Interestingly, responders were more likely to have platinum sensitive disease, which is increasingly considered a surrogate marker of HR deficiency.

In 2010, the results of phase II studies of olaparib in patients with *BRCA1/2* mutated recurrent advanced ovarian and breast cancer were published, demonstrating ORRs of 33% and 41%, respectively, in heavily pretreated patients who received olaparib at 400mg bid.[31,32] Notably, the breast cancer patients were evenly divided among subtypes, with 50% TNBC, 45% hormone positive, and 4% human epidermal growth factor-2 (HER2) positive. Again, toxicities included mild fatigue and nausea in 40% of patients. Another phase II trial of olaparib in advanced metastatic or recurrent ovarian, *BRCA* mutated breast cancer, or triple negative breast cancer disappointingly observed no responses in any breast cancer patients.[33] However, in addition to the 41% of *BRCA* mutated ovarian cancer patients who responded to olaparib, another 24% of *BRCA* wildtype (WT) ovarian cancer patients responded. A posthoc analysis found that responsiveness in both groups was highly correlated with platinum sensitivity, again

suggesting the utility of platinum sensitivity as a marker for HR deficiency beyond that mediated by *BRCA*.

In 2012, results of a randomized double blind phase II study of olaparib maintenance in patients with advanced ovarian cancer were published. Although olaparib improved progression-free survival (PFS), no improvement in OS was seen.[34] An interim analysis two years later specifically examined patients with somatic and germline *BRCA* mutations, finding a significantly improved PFS for *BRCA* mutated patients. Still, no difference on OS was observed for those assigned to olaparib maintenance.[35] However, a 2015 phase II study of olaparib in patients with germline *BRCA1/2* mutations found that the drug had promise in multiple tumor types, demonstrating ORRs of 12.9%, 31.1%, 21.7%, and 50% in patients with breast, platinum resistant ovarian, pancreatic, and prostate cancers, respectively.[36] In 2014, updated results of the phase II study of olaparib in *BRCA1/2* mutated recurrent advanced ovarian cancer were released, demonstrating an ORR of 34% and median duration of response (DoR) of 7.9 months in patients who had received three or more prior lines of chemotherapy.[37] As a result, the Food and Drug Administration (FDA) approved the use of olaparib in this patient population.[38]

The potential of single agent olaparib in breast cancer was demonstrated in 2017 in the OlympiAD study, a randomized, open label, phase III trial of olaparib versus standard of care (SOC) chemotherapy in patients with germline *BRCA* mutated, HER2-negative MBC.[39] The trial found an improved response rate in the olaparib group (59.9% vs. 28.8% for SOC), as well as improved PFS (7.0 months for olaparib vs. 4.2 months for SOC). No difference was observed in OS, although the study was not powered to detect this, nor was it powered to differentiate among outcomes in patients stratified by hormone-receptor positive disease or history of platinum use. Nevertheless, this was the first phase III trial to definitively demonstrate a small but clear benefit of olaparib use in heavily pretreated patients with *BRCA1/2* mutated MBC.

Patients on this trial will be treated with olaparib 300 mg q12hrs each day of a 28-day cycle in tablet formation until disease progression, unacceptable toxicity, withdrawal of consent or death. Tablet formation is preferred over capsule formulation based on recent work demonstrating equivalent efficacy with a reduced pill burden.[40]

2.3.1.1 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib Investigator's Brochure.

2.3.1.2 Toxicology and safety pharmacology summary

The toxicology and safety pharmacology is fully described in the current version of the olaparib Investigator's Brochure.

2.3.1.3 Clinical experience

This section lists those ADRs that are currently regarded as expected for regulatory

reporting purposes.

Olaparib monotherapy has been associated with laboratory findings and/or clinical diagnoses, generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation.

The safety profile is based on pooled data from 1248 patients treated with olaparib monotherapy in clinical trials in the therapeutic indication at the recommended dose.

The following adverse reactions have been identified in completed clinical trials with patients receiving olaparib monotherapy where patient exposure is known. Adverse Drug Reactions are organized by Medical Dictionary for Regulatory Activities (MedDRA) SOC and then by MedDRA preferred term. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000) including isolated reports.

Adverse Drug Reactions reported in Clinical Trials

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE Grade 3 and above
Blood and lymphatic system disorders	Anaemia[a]	Very common	Very common
	Neutropenia[a]	Common	Common
	Thrombocytopenia[a]	Common	Common
	Leukopenia[a]	Common	Common
	Lymphopenia[a]	Uncommon	Uncommon
Immune system disorders	Rash[a]	Common	-
	Hypersensitivity[a]	Uncommon	-
	Dermatitis[a]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Common
	Nausea	Very common	Common
	Dyspepsia	Very common	-
	Stomatitis	Common	Uncommon
	Upper abdominal pain	Common	Uncommon
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Increase in creatinine	Common	Uncommon
	Mean corpuscular volume elevation	Uncommon	-

[a] Anaemia includes PTs of anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased and neutrophil count decreased, febrile neutropenia and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased and plateletcrit decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash and generalised erythema; Hypersensitivity includes PTs of hypersensitivity and drug hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis

CIOMS Council for International Organizations of Medical Sciences; CTCAE Common Terminology Criteria for Adverse Events v.3.0; MedDRA Medical Dictionary for Regulatory Activities; SOC System organ class.

Description of selected adverse reactions

<u>Hematological toxicity</u>

Anemia and other hematological toxicities are generally low grade (CTCAE Grade 1 or 2). However, there are reports of CTCAE Grade 3 and higher events. Anemia was the most common CTCAE Grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with olaparib, the incidence of CTCAE Grade ≥2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leukocytes 20% (all % approximate).

The incidence of elevations in MCV from low to normal at baseline to above the upper limit of normal was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences. Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment with olaparib, and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.

Other laboratory findings

In clinical studies with olaparib, the incidence of CTCAE Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 15%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae; 90% of patients had creatinine values of CTCAE Grade 0 at baseline and 10% were CTCAE Grade 1 at baseline.

Nausea and vomiting

Nausea was generally reported very early, with first onset within the first month of olaparib treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of olaparib treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients.

Combination studies

Safety data from studies in which olaparib has been administered in combination with other agents are discussed below. The degree of bone marrow suppression observed in some patients in the combination studies has however been greater than would be expected with the chemotherapy agent alone, as per label information. Myelotoxicity has been observed in studies evaluating olaparib with the following combination therapies: DTIC; carboplatin; paclitaxel; carboplatin + paclitaxel; gemcitabine; topotecan; cisplatin; doxorubicin, cisplatin + gemcitabine; or irinotecan.

The principal hematological toxicities observed have been neutropenia, thrombocytopenia, and anemia. These findings are consistent with pre-clinical

findings.[24,41–43]

Safety: combination studies

Administration of olaparib in combination with DTIC, topotecan, paclitaxel, carboplatin and paclitaxel, cisplatin and gemcitabine resulted in a lower MTD compared with administration of olaparib as a monotherapy. Olaparib doses ranging between 20 mg bd and 200 mg bid in combination with these other treatments resulted in an increase in myelotoxicity, especially neutropenia. In some cases this was despite administration of sub-optimal doses of olaparib and a reduction in the suggested dose of the combination study drug (eg, topotecan). Administration of bevacizumab at recommended doses with olaparib up to 400 mg bd was a well-tolerated combination treatment resulting in no unusual or unexpected AEs. Olaparib in combination with liposomal doxorubicin 40 mg/m2 was generally well tolerated at dose levels ranging from 50 mg bd to 400 mg bd, with both a 7-day and a 28-day dosing schedule.

Adverse events of special interest

Myelodysplastic syndrome/acute myeloid leukemia

The incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was <1.5% and the majority of events had a fatal outcome. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging treatments. The majority of reports were in germline BRCA mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that olaparib should be discontinued and the patient be treated appropriately.

New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents.

Pneumonitis

Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When olaparib was used in clinical studies in combination with other

therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or anabnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.

Clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure.

2.3.2 AZD6738

Investigators should be familiar with the current AZD6738 Investigator's Brochure. AZD6738 is a potent, selective inhibitor of the serine/threonine-specific protein kinase, ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. ATR is an atypical kinase in one of the DNA-damage induced checkpoint pathways, and during normal DNA replication is recruited at stalled replication forks, which can progress to double strand breaks if left unrepaired. Following resection of double strand breaks ATR is recruited to single strand DNA coated with Replication Protein A (RPA) following single strand DNA damage. Recruitment and activation of ATR leads to cell cycle arrest in the S phase while the DNA is repaired and the stalled replication fork resolved, or nuclear fragmentation and entry into programmed cell death (apoptosis). Loss of ATR function leads to the inability to resolve stalled replication forks, the accumulation of DNA damage and rapid cell death exemplified by nuclear fragmentation.[24,41–43] AZD6738 is being developed as an oral anti-tumor agent with an initial focus on patients with ATM-deficient disease, although there is preclinical evidence for activity in broader malignant disease types.

In patients with malignancies, an ATR inhibitor has the potential to have monotherapy activity, through synthetic lethality[44] or combination activity, by leading to dependency on other mechanisms of DNA damage repair which may be targeted by other DNA damaging agents or inhibitors of DNA repair such as PARP inhibitors.

Patients on this trial will be treated with AZD6738 160 mg qday on days 1-7 of a 28-day cycle in tablet formation until disease progression, unacceptable toxicity, withdrawal of consent or death.

2.3.2.1 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the AZD6738 Investigator's Brochure.

2.3.2.2 Toxicology and safety pharmacology summary

The toxicology and safety pharmacology is fully described in the current version of the AZD6738 Investigator's Brochure.

2.3.2.3 Clinical experience

This section lists those ADRs that are currently regarded as expected for regulatory reporting purposes.

Adverse effects for patients who have received AZD6738 is available for those treated on four clinical trials. **D5330C00001** (NCT01955668) was a two-part phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary anti-tumor activity of multiple ascending doses of AZD6738 in patients with prospectively identified 11q-deleted relapsed/refractory chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL) or B cell lymphomas. One 70 year old male patient, with 11q deleted CLL, has been dosed with AZD6738 (20 mg BD, 3weeks on/ 1 week off) for one cycle (28 days); study treatment was stopped due to disease progression. This study was stopped due to difficulties in recruiting the required patient population. Only one patient was treated on study.

PATRIOT (D5330C00002) was a study of AZD6738 in advanced solid malignancies sponsored by the Royal Marsden Hospital and Institute for Cancer Research in London. The study opened to recruitment in June 2014 and has now terminated recruitment. The study comprises 3 parts: Part A, a monotherapy dose escalation in patients with advanced solid malignancies, who have exhausted other treatment options; Part B, a monotherapy expansion in prospectively selected ATM-deficient advanced solid cancer patients, to examine one or more schedules of AZD6738; and Part C, a radiotherapy combination expansion.

As of the February 2019, forty-six patients enrolled and received at least 1 dose AZD6738 on the PATRIOT study. Patients received one of two different schedules at the established MTD of 160 mg BD. Seventeen of twenty-six (65%) patients in dose escalation and 7/20 (35%) in dose-expansion had Grade ≥ 3 treatment-related adverse events (TRAEs). An intermittent schedule (2-week-on, 2-week-off) was better tolerated than continuous dosing, with Grade ≥ 3 TRAEs in 4/6 (67%) receiving continuous and 3/15 (20%) with intermittent dosing. The most common TRAEs were fatigue, anaemia, nausea and thrombocytopenia; Five (19%) patients in dose-escalation and 1 (5%) in dose-expansion discontinued due to toxicity. Best overall response was confirmed partial response (PR) in 3 (7%) participants, unconfirmed PR in 1 (2%), stable disease (SD) in 22 (48%) and PD in 12 (26%).[64]

VIKTORY is an externally sponsored basket study that is examining novel agents in combination with paclitaxel in 2nd line gastric cancer. Patients were assigned to treatment arms based upon the molecular profile of their tumor. The study was sponsored by the SAMSUNG Medical Center in Korea and the PI was Dr. Jeeyun Lee. In the phase 1 part of the study, eligible patients with solid tumors received escalating doses of ceralasertib in combination with a fixed dose of paclitaxel (80 mg/m2 on D1, D8, D15) in 28-day cycles. The dose of ceralasertib was escalated to

reach an MTD in a rolling 6 design. The starting dose of ceralasertib was 40 mg QD. Fifty-seven patients were enrolled in 7 dose cohorts ranging from 40 mg QD to 240 mg BD plus weekly paclitaxel. The RP2D was established as ceralasertib 240 mg BD days 1–14 plus paclitaxel 80 mg/m2 on D1, D8, D15 every 28 days. Cytopenias were the most common toxicity. With neutropenia in 39 patients (68%) anemia in 25 patients (44%), and thrombocytopenia in 21 patients (37%). In the full analysis set of 57 patients, the overall response rate (ORR) was 22.6% (95% CI, 12.5–35.3).[65]

Study **D5330C00004** (NCT02264678) is an ongoing modular, phase I, 2 part, open-label, multicentre study of AZD6738, administered orally, in combination with cytotoxic chemotherapy regimens or novel anticancer agents, to patients with advanced/metastatic solid malignancies. The study design allows an escalation of the dose of AZD6738 as monotherapy and in combination with the standard dose and schedule of either cytotoxic chemotherapies or novel anti-cancer agents, with intensive safety monitoring to ensure the safety of the patients.

The first module, Module 1, of the study is investigating AZD6738 administered orally in combination with Carboplatin, to patients with advanced malignancies in order to establish the minimally biological active dose of AZD6738, with subsequent expansions in patients with ATM deficient Non-Small Cell Lung Cancer.

The second module, **Module 2**, of the study is investigating **AZD6738 administered orally in combination with olaparib**, to patients with advanced malignancies. The purpose of this module is to establish the MBAD of AZD6738 given in combination with olaparib, and assess preliminary efficacy in a subsequent expansion(s) in patients with advanced ATM-deficient gastric adenocarcinoma (including the gastrooesophageal junction).

The third module, Module 3, of the study is investigating AZD6738 administered orally in combination with MEDI4736, to patients with advanced Non-Small Lung Cancer (NSCLC) or Head and Neck Squamous Cell Carcinoma (HNSCC) with a subsequent expansion in HNSCC patients to assess preliminary efficacy. By the data lock point of this report (13th June 2016) 67 patients had received at least one dose of AZD6738 in the AstraZeneca-sponsored clinical development programme study D5330C00004. These are broken down as follows:

- Thirty two (32) patients have received AZD6738 in combination with carboplatin
- Twenty Seven (27) patients have received AZD6738 in combination with olaparib
- Eight (8) patients have received AZD6738 in combination with the anti-PDL1 antibody, durvalumab

Several dose levels and schedules in each module have been investigated during this reporting period. Details of the first and third cohorts are contained in the module specific tables below:

Module 1 – in combination with Carboplatin AUC 5

Cohort	Dose level	Dose frequency	Schedule (21day cycle)	Key AE observations
1	20mg	BD	Days 4 to 20	Not tolerated. G3 thrombocytopenia leading to delay of cycle 2 of study treatment G3 fatigue
2	20mg	BD	Days 4 to 13	Not tolerated G3 thrombocytopenia leading to delay of cycle 2 of study treatment
3	20mg	BD	Days 4 to 10	Tolerated G3 neutropenia, G4 thrombocytopenia
4	40mg	BD	Days 4 to 10	Tolerated G3 neutropenia, G4 thrombocytopenia
5	60mg	QD	Days 4 to 10	Not tolerated G4 thrombocytopenia
6	60mg	QD	Days 1 to 3	Not tolerated G3 neutropenia, G4 thrombocytopenia
7	40mg	QD	Days 1 to 2	Cohort ongoing at time of data cut

G3 thrombocytopenia leading to a delay in subsequent cycles has been observed in cohorts 1-5.

Module 3 – Combination with Durvalumab

8 patients have been treated with 1500mg durvalumab (Day 1 of a 28 day cycle) combined with AZD6738 dosed for 80mg BD for 14 days as a monotherapy run-in then days 22 to 28 of each subsequent cycle. No attributable adverse events greater than CTCAE G2 have been reported.

2.3.2.4 Clinical experience of AZD6738 in combination with olaparib

Module 2 of study **D5330C00004** (NCT02264678) has examined AZD6738 alone and in combination with olaparib.

The purpose of this module is to establish the Recommended Phase 2 Dose (RP2D) of AZD6738 given in combination with olaparib (Part A), and assess preliminary efficacy in a subsequent expansion(s) in patients with advanced ATM-deficient gastric adenocarcinoma (Part B1), ATM-proficient gastric adenocarcinoma (Part B2), breast cancer patients with BRCA mutations (somatic or germline) excluding HER2-positive breast cancer patients (Part B3) and TNBC patients with no known BRCA mutations (Part B4). Five doses and schedules were explored, and results were first reported in November 2016, at which time 27 patients had been treated. When AZD6738 was given for 14 days, 1 patient experienced G4 thrombocytopenia and 2 patients experienced G3 neutropenia. With shorter durations of AZD6738, the combination regimen was better tolerated.[45]

This study was last presented at the AACR annual meeting in April 2018, at which time 45 patients had been treated with the combination of olaparib and AZD6738. Grade ≥3 adverse events occurring in ≥20% of patients included thrombocytopenia (5 patients), anemia (7), neutropenia (6), fatigue (1), anorexia (1), nausea, vomiting, constipation, diarrhea, and cough. Dose-limiting toxicities were thrombocytopenia and neutropenia. Among 39 evaluable patients, 1 patient had a comprete response, 5 had partial responses, and 1 patient had an unconfirmed partial response; all patients had *BRCA1/2* mutations.[46] Multiple expansion cohorts are still enrolling (NCT02264678).

Several trials of the combination of olaparib and AZD6738 are ongoing. These include NCT03462342, a phase 2 study in recurrent ovarian cancer; NCT03428607, a phase 2 study in relapsed small cell lung cancer; NCT03330847, a phase 2 study in metastatic triple negative breast cancer; NCT02937818, a phase 2 study in platinum refractory extensive stage small cell lung cancer; NCT02576444, a phase 2 study in advanced solid tumors with mutations in genes required for homologous recombination DNA repair; and NCT02264678, a phase 1/2 study of the combination in advanced solid malignancies.

2.3.2.5 Determination of recommended phase 2 dose of AZD6738 in combination with olaparib

The Recommended Phase 2 Dose for expansion has been declared as AZD6738 160 daily D1-7 with olaparib 300 mg BID continuously based on preliminary results from NCT02264678, a phase I study of AZD6738 in combination with multiple anti-cancer agents including olaparib, as described above in Section 2.3.2.4. Dose-limiting toxicities were thrombocytopenia and neutropenia.[46]

The AZD6738 dosing schedule of 7 days on, 21 days off within each treatment cycle was supported by the PK-PD model of thrombocytopenia, predicting a period of 21 days free of drug to achieve a full platelet recovery. The recommended dose 160 mg OD was predicted to maintain AZD6738 mean steady state concentrations above the estimated IC90 threshold (based on ATR enzyme inhibition assay in LoVo cells) and the GI90 threshold (based on the cellular growth inhibition activity in LoVo cells) across the full dosing interval i.e 24 h. Please refer to the AZD6738 Investigator's Brochure for further information around the in-vitro threshold values. In addition, this daily dose level was associated with a decrease in peripheral monocytes in most of the patients and the preliminary blood cell count data from D5330C00004 and D5330C00002 studies suggested this decrease to be AZD6738 specific and dose dependent (monocyte decrease was not observed with either single agent olaparib or durvalumab). Monocytes have been characterized as being deficient in DNA base excision repair and PARP1 expression,[47] suggesting an on-target synthetic lethal effect of AZD6738 mediated ATR inhibition in this cell type. Utilizing the monocyte decrease as a quantitative measure of AZD6738 pharmacological activity, the recommended Phase 2 dose of 160mg OD D1-7 was driven by maintaining

maximally active exposure consistent with manageable safety.

2.4 Correlative Studies Background

2.4.1 Rationale for CLIA laboratory confirmed IDH1/2 mutation

IDH1/2 mutations are necessary for enrollment on the study because patients whose tumors harbor these mutations are a specific sub-population that we hypothesize will derive clinical benefit from PARP inhibition. These mutations can be established histologically or via standard sequencing methods available at a CLIA-certified pathology laboratory or a commercial entity, which is now considered a standard feature of pathology reports for solid tumors. Examples of centers/commercial laboratories with this capability include the Mayo Clinic (http://www.mayomedicallaboratories.com/test-catalog/Overview/35854), MDACC (https://www.mdanderson.org/research/research-resources/core-facilities/molecular-diagnostics-lab/services/idh1-mutation-analysis.html), and Foundation Medicine. This approach to select patients is commonly used in several recent and ongoing clinical trials focused on IDH1/2-mutant tumors (e.g., NCT02454634, NCT02771301, NCT02381886, NCT02826642, NCT02074839, NCT02746081, NCT01915498, NCT02481154).

If a patient has an archived tumor specimen that has not been tested for tumor profiling, which includes evaluation of IDH1/2 mutations, his or her physician may do so at any time outside the bounds of this clinical trial, a process that typically takes 2-4 weeks. Should a qualifying IDH1/2 mutation be found in that patient's tumor, this would make the patient preliminarily eligible to participate in the trial.

Only specific mutations that lead to a neomorphic phenotype will be eligible for enrollment, and include those listed below:

IDH1: R132V, R132G, R132S, R132L, R132C and R132H
IDH2: R140W, R140L, R140Q, R172W, R172G, R172S, R172M, R172K

Whole exome sequencing and RNA sequencing, which includes IDH analysis, will be performed prior to study completion for the purpose of data analysis. This analysis will be performed on pre-treatment biopsy tissue and archival formalin-fixed paraffin embedded (FFPE) specimens, if the latter is available. If a patient opts out of pre- and on-treatment biopsies, that patient must have an adequate archival specimen to enroll on the trial and this specimen will be analyzed.

2.4.2 Rationale for LC-MS detection and quantification of 2HG in plasma and tissue biopsies

In view of its role as the central oncometabolite in IDH-mutated tumors, we seek to determine whether 2-HG can potentially serve as a non-invasive biomarker of disease burden and response to treatment. We hypothesize that radiographic response to treatment will correlate with elevated pre-treatment tumor and plasma 2HG levels. In patients who respond to treatment, we hypothesize that a decrease in plasma 2HG levels will be

observed.

Our study focuses on tissue and plasma evaluation of 2HG using liquid chromatography-mass spectrometry (LC-MS). In 2009, Dang et al. first used LC-MS to demonstrate that IDH1 mutated human glioblastoma tumors were characterized by significantly elevated levels of 2HG (as high as 35mM) compared to WT samples (<0.1 mM).[48] More recently, LC-MS was used to demonstrate elevated tissue 2HG levels in patients with IDH1/2 intrahepatic cholangiocarcinoma. In two IDH1/2 mutated frozen intrahepatic cholangiocarcinoma specimens, tissue levels of 2HG were significantly elevated (849.9 μg/g and 588.5 μg/g) when compared to compared to three WT specimens (average 3.41 μg/g).[4]

The value of plasma 2HG measurement has been well demonstrated in AML. In a study of 223 patients with de novo AML, 97% of mutant IDH1/2 AML samples had a 50-fold higher 2HG concentration in their sera (median, 3004 vs. 61 ng/mL, $P < 0.0005$).[49] Interestingly, 2-HG levels of >700 ng/mL could successfully differentiate patients with IDH1/2 mutations from those with WT malignancies. Further, 2-HG levels of >200 ng/mL after therapy correlated with a shorter overall survival compared with patients with plasma 2HG levels <200 ng/mL (hazard ratio, 3.9; $P = 0.02$), illustrating the value of following this biomarker throughout treatment.[49]

Several small studies have shown mixed results with plasma 2HG measurement in solid tumors. A 2012 study of 16 patients with gliomas, plasma levels of 2HG measured by GC-MS were not significantly higher in the ten patients with IDH1/2 mutated tumors, although a trend toward elevated levels was observed.[50] More recently, studies of 38 and 44 patients with IDH1/2mt gliomas compared to 46 and 16 WT patients, respectively, demonstrated no significant difference in mean plasma 2HG concentrations.[51,52]

There is stronger evidence that 2HG plasma levels are elevated in patients with IDH1/2 mutated cholangiocarcinoma. One study demonstrated that plasma levels of 2HG were significantly elevated in 11 patients with IDH1 mutant intrahepatic cholangiocarcinoma (median, 478 ng/mL) when compared to 20 IDH1/2 WT controls (median, 118 ng/mL, $P < 0.0001$).[53] Plasma 2HG levels >= 170 ng/mL could predict the presence of an IDH1/2 mutation with a sensitivity of 83% and a specificity of 90%. These findings were verified in a validation cohort of 38 patients. Additionally, circulating 2HG levels were felt to correlate directly with tumor burden.

The relationship between plasma and tissue 2HG levels is unclear. Early data suggests that plasma and tissue levels of 2HG are correlated in AML; the extent of their correlation in solid tumors is unknown.[54,55] However, when LC-MS was used in the case of a patient with IDH1 mutated metastatic adenocarcinoma of the breast, plasma and urine 2HG levels were markedly elevated compared to those of six WT patients.[56] Our proposed study enrolling at least 28 patients with IDH mutant tumors will allow us to test our hypotheses radiographic response to treatment will correlate with elevated pre-treatment tumor and plasma 2HG levels and that a decrease in plasma 2HG levels will be observed in patients who respond to treatment. It will also provide compelling evidence

for whether plasma levels of 2HG correlate well with tissue levels and thus can potentially serve as a useful and noninvasive predictor of response in solid tumors.

2.4.3 Rationale for RNA sequencing and DNA sequencing

Whole-exome DNA sequencing will be performed on tumor biopsy tissue to determine if other co-occurring genomic alterations potentiate, or interact with, the effects of IDH1/2 mutations and oncometabolites, leading to differences in the efficacy of olaparib and AZD6738. DNA will be extracted from fresh frozen biopsies obtained before and during therapy and from archival specimens for those patients who opt out of biopsies. Mutations and copy number variants will be assessed to measure genomic correlates of response or resistance to therapy in the setting of IDH1/2 mutations.

Beyond examining co-occurring mutations, we will use the sequencing data to analyze copy number alterations and mutational signatures that have been previously associated with homologous recombination deficiency.[57–59] For example, specific patterns of allele-specific copy number alterations have been associated with homologous recombination deficiencies.[59] We will also use the sequencing data to attempt to identify novel mutational and genomic signatures that may be associated with an IDH1/2 mutation-induced HR deficiency in particular.

For the same reasons noted above, we will use RNAseq on our paired biopsy specimens to monitor gene expression and transcriptome changes during treatment with olaparib and AZD6738. This will allow us to detect changes in gene expression patterns and to characterize multiple forms of noncoding RNA.

2.4.4 Rationale for assessing markers of DNA damage in tumor biopsies

As presented above, our collaborators have identified an activated DNA damage response in IDH1/2-mutant cells, which includes elevated γH2AX and 53BP1 foci at baseline, in the absence of DNA damage. They have also found that inhibition of either PARP or ATR in IDH1/2 mutated cell lines resulted in the accumulation of DNA double strand breaks as measured by γH2AX and 53BP1 foci. Evidence of increased DNA damage, particular DNA double strand breaks, in patient samples after treatment with olaparib in combination with AZD6738 would thus demonstrate proof of enhanced DNA double strand breaks and serve as proof of mechanism.

DNA damage signals associated with HRD can be recognized in conventional biopsy tumor samples by selective detection of targets associated with DNA repair. For example, γH2AX is a sensitive marker for DNA DSBs.[60] Specifically, spatially resolved measurement of DNA-repair targets using in situ methods can report on the magnitude of DNA stress using minimum amounts of tissue and map specific location of signal within the tumor bed.

As such, we will use multiplexed quantitative immunofluorescence (mQIF) and CyTOF-IMC based panels to test whether we can detect these changes in pre-treatment and on-treatment tumor biopsies. Markers included in the mQIF/IMC panels will include tumor

cell markers (cytokeratin, GFAP), HRD-related sensors (γH2AX, p53BP1, NBS1) and eventually also mutant IDH proteins or immune cell markers. We will also expand our studies to look at multiple DNA damage response proteins and post-translational modifications. Protocols and strategies for mQIF on histology preparations from intact tumor specimens has been extensively performed and reported by the Schalper Laboratory at Yale.

Mass Cytometry Time of Flight (CyTOF) has emerged as a powerful technique for multiparameter single cell analysis.[61] The approach uses heavy metal ions as antibody labels, which overcomes many limitations associated with fluorescence-based cytometry. As such, dozens of unique molecular features can be analysed on single cells, which allows for detailed molecular profiling and assessments of tumor heterogeneity.[62] More recently, this technique has been coupled to immunohistochemical and immunocytochemical methods with high-resolution laser ablation.[63] This new approach allows one to image proteins and/or protein modifications at subcellular resolution, in frozen and FFPE tissue specimens. Yale has acquired the CyTOF Imaging Mass Cytometry (IMC) platform for this technique and has standardized assays for its use on clinical-grade fresh frozen and FFPE specimens.

As such, we will use CyTOF-IMC to test whether we can detect these changes in pre-treatment and on-treatment tumor biopsies.

2.4.5 Rationale for assessing RAD51 foci

A crucial event during Homologous Recombination (HR)-mediated DNA repair is the formation of the RAD51 nucleofilament at sites of double-strand breaks. These structures appear as sub-nuclear foci when detected by a RAD51 specific antibody and the presence of such sub-nuclear RAD51 foci is a surrogate functional marker for HR status. In addition, HR-mediated DNA repair is restricted to cells in the S-phase of the cell cycle. Therefore, by staining for Geminin, a marker for cells in S-phase, and RAD51, it is possible to rapidly determine the functional status of HR in the sample.

3. PATIENT SELECTION

3.1 Eligibility Criteria

1. Subjects must be able to understand the nature of this trial and provide written informed consent, prior to any study specific procedures. Patients with Impaired Decision Making Capacity (IDMC) who have a close caregiver or Legally Authorized Representative (LAR) may be considered eligible for this study at the treating Physician's discretion, provided that the Physician is reasonably sure that the possible risks and benefits of the study are clear and that the patient will take the drug as prescribed.

2. Subjects must be diagnosed with a solid malignant tumor (other than cholangiocarcinoma or primary CNS tumor) that has progressed despite standard therapy, or for which no

effective standard therapy exists. Patients with cholangiocarcinoma are no longer allowed as this cohort has closed to accrual. Patient with primary CNS tumors, e.g. glioma, are not allowed.

3. Patients must have biopsy-confirmed evidence of an IDH1 or IDH2 mutation, confirmed in a CLIA-certified laboratory, associated with neomorphic activity of the encoded proteins. See Section 2.4.1 for additional information on IDH1/2 mutation confirmation and those that are neomorphic.

4. Patients must have tumors determined to be easily accessible for biopsy and must be willing to have serial biopsies. Tumor biopsies will be performed on the most accessible biopsable site of disease. All possible precautions to avoid complications will be taken, including discussions in multidisciplinary meetings, if needed. If a patient opts out of a pre-treatment biopsy, biopsy is not possible, or if a pre-treatment biopsy does not yield sufficient tissue for analysis, the patient must be willing to provide an sufficient archival FFPE specimen for LC/MS analysis of 2HG in order to enroll on the study. Permission of the study PI is required in all of the above scenarios.

   In order to maximize the availability of newly obtained specimens for 2-HG analysis, at least 10 biopsies will be required in each group (cholangiocarcinoma and other solid tumors) of 14 patients treated in the first stage of this Simon two-stage design. Thus if 4 patients in an arm have already opted out, further patients may only enroll on that arm (in the first stage) if they agree to undergo the pre- and on-treatment biopsies. If a patient has agreed to undergo the two biopsies and undergoes the pre-treatment biopsy, he or she may not opt out of the second biopsy unless such a biopsy would not be safe (e.g. inaccessible tumor). Permission of the study PI is required in this scenario.

   All patients must be willing to provide 5 unstained archival slides, if available, for pre-treatment 2-HG analysis and correlation with 2-HG levels in pre-treatment frozen specimens.

5. Patients must be willing to undergo extra blood sampling for correlative studies.

6. Patients must have measurable disease by RECIST v1.1.

7. Patients must have at least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) or ≥ 10 mm with callipers by clinical exam OR at least one lesion (measurable) that can be accurately assessed by CT/MRI/clinical exam at baseline and follow up visits. See Section 12 for the evaluation of measurable disease.

8. Subjects must have progressive cancer at the time of study entry.

9. Prior experimental (non-FDA approved) therapies (other than drugs that target ATR) and immunotherapies are allowed. Patients must not have received these therapies for 30 days

or five half-lives of the drug (whichever is less) prior to the initiation of study treatment.

10. Toxicities from prior therapies should have recovered to ≤ grade 1, with the exception of stable chronic grade 2 toxicities that are not overlapping with presumed toxicities of olaparib.

11. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after central nervous system (CNS)-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT scan) during the screening period.

12. Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required for at least 4 weeks (or scheduled assessment after the first cycle of treatment), and a risk-benefit analysis (discussion) by the patient and the investigator favors participation in the clinical trial

13. If evidence of chronic hepatitis B virus (HBV) infection, HBV viral load must be undetectable on suppressive therapy if indicated. If history of hepatitis C virus (HCV) infection, must be treated with undetectable HCV viral load.

14. Female/male of age ≥18 years. This is because no dosing or adverse event data are currently available on the use of olaparib or AZD6738 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

15. ECOG 0-1 (Karnofsky ≥70%, see APPENDIX A).

16. Patients must have adequate organ and bone marrow function measured within 14 days prior to administration of study treatment as defined below:
    a. Hemoglobin ≥ 10.0 g/dL with no blood transfusion in < 14 days prior to starting therapy
    b. Leukocytes ≥ 3,000/mcL
    c. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    d. Platelet count ≥ 100 x 10^9/L
    e. Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
    f. Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN
    g. Patients must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min or based on a 24 hour urine test:
        - Estimated creatinine clearance = $\frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$ (x F)[a]

        [a] where F=0.85 for females and F=1 for males.

17. No features suggestive of MDS/AML on peripheral blood smear when performed as clinically indicated.

18. Patients must have a life expectancy of ≥ 16 weeks, in the opinion of the treating physician.

19. Patients must be willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

20. Prior radiation therapy is allowed. Patients must not have received radiation therapy within 3 weeks prior to the initiation of study treatment.

21. Women of child-bearing potential are expected to use highly effective contraception during the study and for 6 months after the last dose of study drug. See Appendix E for appropriate methods of contraception. Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1. Postmenopausal is defined as:
    h. Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    i. Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
    j. Radiation-induced oophorectomy with last menses >1 year ago
    k. Chemotherapy-induced menopause with >1 year interval since last menses
    l. Surgical sterilisation (bilateral oophorectomy or hysterectomy)

22. Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination, throughout the period of taking study treatment and for 6 months after last dose of study drug(s) to prevent pregnancy in a partner. See Appendix E for appropriate methods of contraception.

23. Patients with human immunodeficiency virus (HIV) on effective antiretroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2 Exclusion Criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study

2. Previous enrollment in the present study

3. Participation in another clinical study with an investigational product during the last 30 days or five half-lives of the drug (whichever is less) prior to the initiation of study treatment

4. Any previous treatment with a PARP inhibitor.

5. Any previous treatment with AZD6738 or any other ATR inhibitor.

6. Patients receiving any systemic chemotherapy or radiotherapy within 3 weeks prior to study treatment.

7. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with a history of localized triple negative breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.

8. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.

9. Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks.

10. Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

11. Persistent toxicities caused by previous cancer therapy. Toxicities should have recovered to ≤ grade 1, excluding alopecia, or should be stable chronic grade 2 toxicities that do not overlap with presumed toxicities of olaparib and/or AZD6738.

12. Patients with myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) or features suggestive of MDS/AML.

13. Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are not eligible if the treating physician determines that immediate CNS specific treatment **is** required, and a risk-benefit analysis (discussion) by the patient and the investigator **does not favor** participation in the clinical trial. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study if these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have

received definitive treatment for this and evidence of clinically stable disease for 28 days.

14. Major surgery within 2 weeks of starting study treatment. Major surgeries typically require general anesthesia, are associated with an estimated blood loss of >500mL, and require an overnight hospital stay. Examples include laparoscopic surgery, open resection of organs, joint replacements and other orthopedic surgeries, and vascular or intracranial surgeries. Examples of minor surgeries include those performed on an ambulatory basis, cataract surgery, dental surgeries, cutaneous, endoscopic, and arthroscopic procedures. Effects from major surgeries should have recovered to ≤ grade 1, with the exception of stable chronic grade 2 toxicities that are not overlapping with presumed toxicities of olaparib and/or AZD6738.

15. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent and would limit compliance with study requirements.

16. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

17. Women who are actively breast feeding.

18. Patients with a known hypersensitivity to olaparib or AZD6738 or any of the excipients of the products. History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib or AZD6738.

19. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)

20. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable within the last 28 days)

21. Patients who are receiving any other investigational agents.

22. Pregnant women are excluded from this study because olaparib is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with olaparib, breastfeeding should be discontinued if the mother is treated with olaparib.

23. Receiving, or having received during the 14 days prior to first dose, corticosteroids (at a dose > 10 mg prednisone/day or equivalent) for any reason

24. Any of the following cardiac diseases currently or within the last 6 months (by New York Heart Association (NYHA) ≥ Class 2 where applicable):
    - Unstable angina pectoris
    - Congestive heart failure or known reduced LVEF < 55%
    - Acute myocardial infarction
    - Conduction abnormality not controlled with pacemaker or medication e.g. complete left bundle branch block, third degree heart block
    - Significant ventricular or supraventricular arrhythmias e.g. (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

25. Patients at risk of brain perfusion problems, e.g., medical history of carotid stenosis or pre-syncopal or syncopal episodes, history of TIAs

26. Uncontrolled hypertension (grade 2 or above) requiring clinical intervention

27. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as congestive heart failure, unstable angina pectoris, acute myocardial infarction, hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age, conduction abnormality not controlled with pacemaker or medication.

28. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as congestive heart failure, unstable angina pectoris, acute myocardial infarction, hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age, conduction abnormality not controlled with pacemaker or medication.

29. Patients with relative hypotension (<90/60 mm Hg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of > 20 mm Hg

30. Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738

3.3 Inclusion of Women and Minorities

This is an open trial, recruiting adults affected by IDH1/2 mutated solid tumors. This trial will be recruiting women and members of minority groups because these diseases are found in all sexes, age and races.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR): MD, DO, or international equivalent,
- Non-Physician Investigator (NPIVR): advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- Associate Plus (AP): clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts by July 1, 2023 for all users) is required to participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN,
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status,
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster,
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users),
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *LAO-CT018*, and protocol number *10222*,
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Requirements For #10222 Site Registration

- Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
    - This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the *Regulatory* section, and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users).
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.

- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.2 Patient Enrollment Instructions

Patients with neomorphic IDH1/2 mutations identified in a CLIA certified laboratory may be enrolled.

4.3.3 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.4.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.3.5 Registration Notification

When a patient has been enrolled and an initial biopsy date set, please notify the following people so that they can be prepared to receive shipment and reserve time for their research equipment:

- Jing Li, Ph.D.: LiJing@wayne.edu
- NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank): BPCBank@nationwidechildrens.org

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 10 business days. Patients with previously identified IDH1/2 mutation in a CLIA certified laboratory are eligible, but the mutation must be verified prior to study completion in the central laboratory (MoCha, Frederick

National Laboratory for Cancer Research (FNLCR) or the NCLN Genomics Laboratory). If an eligible IDH mutation is not confirmed centrally, those patients will be excluded from the final analysis. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen and Quantity	Send Specimens to:
Pre-treatment (Day -14 to Day -1)		
	• 10 mL blood in EDTA tube • 3 tissue cores in formalin-containing jars[1] If unable to collect a new biopsy, then submit formalin-fixed, paraffin-embedded (FFPE) archival tissue[2] from the primary tumor: – 1 FFPE block (preferred), OR – Slides from 1 FFPE block (serially sectioned and numbered; 1 H&E stained slide, 40 unstained, uncharged, unbaked 10-micron slides, 2 5-micron slides)	EET Biobank
	• 3 flash frozen tissue cores[1] • 4 mL blood in purple top EDTA tubes[3], processed for plasma (4 aliquots) & buffy coat, and frozen • FFPE archival tissue from the primary tumor: 5 unstained 10-micron slides, if available[2]	Pharmacology Core at Karmanos Cancer Institute
After Cycle 1/Week 4 (+ / - 7 days)		
	• 3 tissue cores in formalin-containing jars[1]	EET Biobank
	• 3 flash frozen tissue cores[1]	Pharmacology Core at Karmanos Cancer Institute
Cycle 2 Day 1 (prior to olaparib dosing)		
	• 4 mL blood[3] in purple top EDTA tubes, processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core at Karmanos Cancer Institute
Cycle 4 Day 1 (prior to olaparib dosing)		
	• 4 mL blood[3] in purple top EDTA tubes, processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core at Karmanos Cancer Institute
Cycle 8 Day 1 (prior to olaparib dosing)		
	• 4 mL blood[3] in purple top EDTA tubes, processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core at Karmanos Cancer Institute
End of Study/Progression/Relapse		
	• 4 mL blood in purple top EDTA tubes[3], processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core Karmanos Cancer Institute

[1]For new biopsies, the Tissue Biopsy Verification Form (Appendix G, Section 8), a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank.

[2] For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. If a patient does not consent to biopsies and only a block is available the site should cut 5 slides for 2HG and send these to Dr. Li, and send the remainder of the block to the biorepository for use by MoCha, Frederick National Laboratory for Cancer Research (FNLCR). If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 46).

[3] Draw blood prior to olaparib dosing.

5.2 Specimen Procurement Kits and Scheduling

Refer to Appendix G, Lab Manual.

5.3 Specimen Collection

Refer to Appendix G, Lab Manual.

5.4 Specimen Tracking System Instructions

Refer to Appendix G, Lab Manual.

5.5 Shipping Specimens from Clinical Site to the EET Biobank

Refer to Appendix G, Lab Manual.

5.6 Shipping of Specimens from Clinical Site to Other Laboratories

Refer to Appendix G, Lab Manual.

5.7 Correlative Studies

Patients will undergo tumor biopsies for integrated and exploratory correlative studies prior to starting therapy and at specific timepoints. The tumor tissue will be obtained by a surgical or imaging guided biopsy (most likely) procedure. Tissue will be obtained at the following timepoints: pre-treatment (within ≤ 2 weeks prior to cycle 1 Day 1 of treatment) and after cycle 1 of treatment (4 weeks, +/- 7 days), as long as the patient has received a minimum of 1 cycle of treatment (or 21 of 28 days of treatment, given the +/-7 day window). Ideally each biopsy will consist of 6 passes of a large gauge needle (such as 16 or 18g) for core biopsy.

For all patients, 5 unstained archival FFPE slides, if available, will be used to evaluate tissue 2-HG levels at time of diagnosis.

We will practice an opt-out policy, wherein a patient may opt out of pre- and post-treatment biopsies. In this case, as well as in circumstances in which biopsy does not yield sufficient tissue for analysis or is not feasible to perform, archival formalin-fixed paraffin embedded (FFPE) specimens will be used, if possible, for pre-treatment LC-MS measurement of 2HG levels in tumor. In the three above scenarios, explicit permission of the study PI is required.

Prioritization for use of tumor tissue specimens will be as follows:

1. DNA whole exome sequencing
2. RNA sequencing
3. mQIF (including IF to look at g-H2AX and RAD51)
4. CyTOF (Schalper lab)
5. 2-HG measurement
6. RAD51 assay

NOTE: For each set of biopsies, 3 of the tumor cores will be formalin-fixed on site and sent to the EET Biobank, where they will be processed. 3 of the tumor cores will be flash frozen on site and sent directly to the Jing Li laboratory at the Karmanos Cancer Institute. Please see Appendix G, Laboratory Manual for details on sample collection, handling and shipping.

These samples then will be distributed to the appropriate locations in the optimal formats, for the studies proposed below, based on the aforementioned tissue prioritization plan.

All patients will undergo additional blood withdrawals for LC-MS detection and quantification of 2HG in plasma.

Any remaining specimens received at the EET Biobank will be banked long-term.

Our overall correlative and biomarker assay process flow and priority list is presented below.

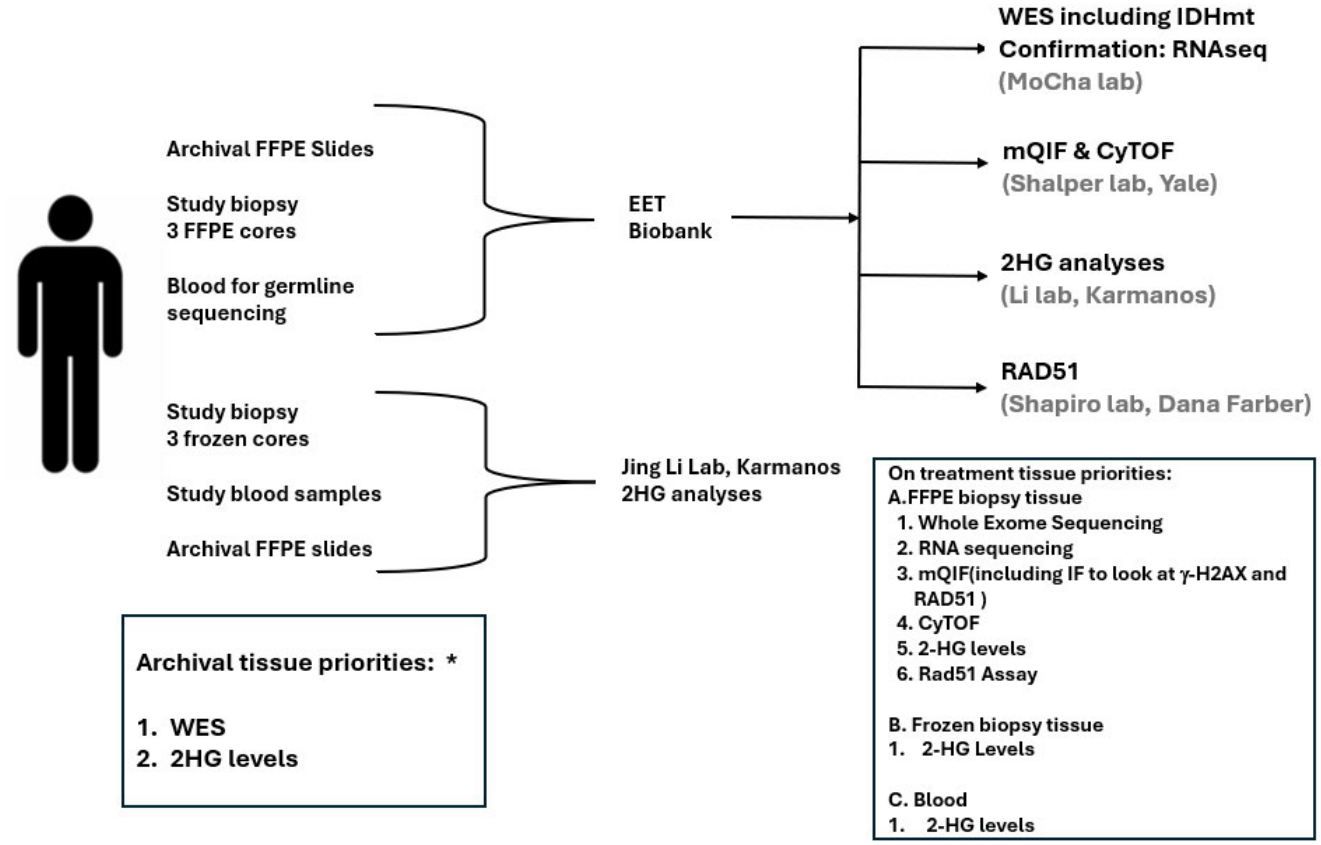


Figure 7. Patient sample and biomarker diagram. * Note: No archival or frozen tissue specimens were received directly by the Li Laboratory. Instead, (per Amendment 13 [version April 4, 2025]), the 2-HG assay will be performed using remaining FFPE tissue that was sent to the EET Biobank

List of Biomarker Assays in Order of Priority

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The tissue/body fluid tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing

Priority	Biomarker Name AND Lab PI and Site	Assay (CLIA: Y/N)	Use (Integral, Integrated, or Exploratory) AND Purpose	Tissue/Body Fluid Tested and Timing of Assay	M/O
Tissue-Based					
N/A	IDH1/2 mutation detection Any commercial lab	Next-generation sequencing CLIA: Y	**Integral** To screen potential patients (eligibility criterion)	Diagnostic tissue	M
1	WES/RNAseq MoCha Laboratory, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich chris.karlovich@nih.gov	Next-generation sequencing CLIA: N	**Integrated** To confirm IDH1 and IDH2 mutations **Exploratory** To search for biomarkers of response and resistance	DNA and RNA from: Archival tissue or formalin-fixed tissue collected prior to initiation of treatment Formalin-fixed tissue at Week 4 (after cycle 1)	M[a]
2	mQIF Tissue DNA damage response assay Schalper Laboratory, Department of Pathology, Yale University School of Medicine Kurt Schalper, MD, PhD kurt.schalper@yale.edu	Multiplex immunofluorescence including g-H2AX and RAD51 CLIA: N	**Exploratory** To assess changes in DNA damage response in malignant cells induced by olaparib/AZD6738	FFPE tissue specimens Prior to initiation of treatment and after cycle 1	M
3	CyTOF DNA damage repair multiplex Schalper Laboratory, Department of Pathology, Yale University School of Medicine Kurt Schalper, MD, PhD kurt.schalper@yale.edu	Multiparametric flow CLIA: N	**Exploratory** To assess changes in DNA damage repair induced by olaparib/AZD6738	FFPE tissue specimens Prior to initiation of treatment and after cycle 1	M
4	2HG tumor concentrations Karmanos Cancer Institute, Wayne State University School of Medicine Jing Li, Ph.D., LiJing@wayne.edu	LCMS/MS CLIA: N	**Integrated** To address the tumor and plasma concentration of 2HG before and after therapy	Archival FFPE or Frozen tissue specimens* Tissue: Prior to initiation of treatment and after cycle 1; 5 slides archival FFPE tissue *No archival or frozen tissue specimens were received at the Li Laboratory. Instead, assay will use FFPE tissue at the time points above that was sent to the EET Biobank.	M[a]
5	Rad51 Center for DNA Damage and Repair, Dana-Farber Cancer Institute Geoffrey Shapiro, MD, PhD geoffrey_shapiro@dfci.harvard.edu	IHC CLIA: N	**Exploratory** To assess changes in DNA damage repair induced by olaparib/AZD6738	FFPE tissue specimens Prior to initiation of treatment and after cycle 1	M[a]
Blood-Based					

Priority	Biomarker Name AND Lab PI and Site	Assay (CLIA: Y/N)	Use (Integral, Integrated, or Exploratory) AND Purpose	Tissue/Body Fluid Tested and Timing of Assay	M/O
1	2HG plasma concentrations Karmanos Cancer Institute, Wayne State University School of Medicine Jing Li, Ph.D. LiJing@wayne.edu	LCMS/MS CLIA: N	**Integrated** To address the tumor and plasma concentration of 2HG before and after therapy	Plasma Prior to initiation of treatment and on day 1 of cycles 2, 4 and 8 and at time of evidence of progression per study schema (plasma only; -/+ 4 days)	M[a]
2	WES MoCha Laboratory, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich chris.karlovich@nih.gov	Next-generation sequencing CLIA: N	**Integrated** Germline control for tissue-based WES	Germline DNA from blood in EDTA. Prior to initiation of treatment	M[a]

[a] = Patients who opt out of pre- and on-treatment biopsies will not have fresh tissue. However, their archival tissue will be tested for tissue 2-HG concentrations.

5.8 Integral Laboratory Studies

5.8.1 IDH1/2 mutation detection

The Bindra laboratory recently discovered that IDH1/IDH2 mutations induce a homologous recombination (HR) defect that renders tumor cells highly sensitive to inhibitors of poly (ADP-Ribose) polymerase (PARP). IDH1-dependent PARP inhibitor sensitivity has been demonstrated in a range of clinically relevant models, including primary patient-derived glioma cells in culture and genetically-matched tumor xenografts in vivo.

Based on these findings, the efficacy of olaparib in the treatment of IDH1/IDH2-mutant solid tumors will tested in a phase 2 study. Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor that has already been approved as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutations in advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Patients will be recruited from participating ETCTN centers.

To enroll on this study, patients must have biopsy-confirmed evidence of an IDH1 or IDH2 mutation, confirmed in a CLIA-certified laboratory, associated with neomorphic activity of the encoded proteins. These mutations are as follows:

Mutations: IDH1: R132V, R132G, R132S, R132L, R132C and R132H
IDH2: R140W, R140L, R140Q, R172W, R172G, R172S, R172M, R172K

5.9 Integrated Correlative Studies

Patients will undergo tumor biopsies for integrated and exploratory studies pre-treatment and after 1 cycle of treatment (4 weeks). The tumor tissue will be obtained by a surgical or imaging guided biopsy (most likely) procedure. If less than 1 cycle of treatment was received, patients will not undergo a second biopsy procedure. When possible each biopsy will consist of 6 passes

of a large gauge needle (such as 16 or 18g) for core biopsy.

Three tumor cores will be formalin-fixed and sent to the EET Biobank and three will be flash-frozen and sent to the Jing Li Lab at the Karmanos Cancer Institute, where they will be processed and stored.

These samples then will be distributed to the appropriate locations in the appropriate formats, for the studies proposed below, based on the aforementioned tissue prioritization plan.

In addition, patients will undergo additional blood withdrawals pre-treatment and on day 1 of cycles 2, 4, and 8 of therapy for LC-MS detection and quantification of 2HG in plasma.

5.9.1 LC-MS detection and quantification of 2HG in plasma and tissue biopsies

We seek to determine whether 2HG can potentially serve as a noninvasive biomarker of disease burden and response to treatment through serial measurements in patients with IDH1/2 mutant solid tumors. LC-MS/MS will be used to measure 2HG plasma concentration using the methods described above. Pretreatment plasma concentration will be compared to post-treatment concentrations collected on day 1 of cycles 2, 4 and 8 of treatment and at time of confirmed evidence of progression. Change in plasma 2HG concentration will be correlated to radiographic response. We will also compare 2HG concentrations in tumor tissue prior to treatment with pre-treatment plasma levels. We hypothesize that radiographic response to treatment will correlate with decreased plasma 2HG levels. On the rationale for examining 2HG levels in plasma and tissue, see Section 2.4.2.

The LC-MS/MS methods for the quantitation of 2HG has been validated based on the FDA Guidance for Bioanalytical Method validation (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm368107.pdf). Method validation includes the tests of specificity/selectivity, intra-/inter-day precision and accuracy, recovery, short-/long-term stability and freeze-thaw to ensure that the method is specific, sensitive, reliable, and reproducible, and suitable for the intended analytical use.

2HG levels in tumor and plasma will be compared in responders and nonresponders.

5.9.1.1 Collection of Specimen(s)

The concentrations of 2HG will be determined in patient plasma and tumor samples. A pre-treatment and on-treatment biopsy after 1 cycle of treatment will be performed, and blood samples will be collected at predefined time points (see Study Calendar). Archival FFPE samples will be analyzed for all patients, if available. If a patient does not consent to biopsy, biopsy is not possible, or the tissue obtained is insufficient for analysis, archival FFPE samples will be analyzed.

NOTE: No archival or frozen tissue specimens were received at the Li Laboratory as of April 2025. Instead, as of Amendment 13 (version April 4, 2025) of this protocol, this assay will use FFPE tissue collected at pre-treatment and on treatment cycle 1 remaining at EET Biobank following completion of the higher priority assays.

Please refer to Appendix G, Laboratory Manual for specimen collection details.

5.9.1.2 Handling of Specimens(s)

Please refer to Appendix G, Laboratory Manual for specimen handling details.

5.9.1.3 Shipping of Specimen(s)

Please refer to Appendix G, Laboratory Manual for specimen shipping details.

5.9.1.4 Site(s) Performing Correlative Study

Karmanos Cancer Institute
Laboratory of Jing Li
Associate Professor of Oncology
Director, Pharmacology Core
Karmanos Cancer Institute
Wayne State University School of Medicine
4100 John R street
HWCRC/Room 523
Detroit, MI 48201
Phone: 313-576-8258
Email: LiJing@wayne.edu

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 DNA sequencing in tumor biopsies

We seek to determine whether co-occuring genomic alterations or changes in the genome can potentially serve as a biomarker of treatment response or resistance through serial assessment in patients with IDH1/2 mutant solid tumors treated with olaparib and AZD6738. Biopsies pre-treatment and on treatment will be performed in order to compare the baseline gene expression profile of the tumor to the one determined after treatment. DNA will be extracted from formalin-fixed tissue biopsies obtained before and during therapy. Mutations, copy number variants, and sub-clonal architecture will be assessed to measure genomic correlates of response or resistance to therapy in the setting of IDH1/2 mutations. In addition, IDH1/2 mutations will be independently verified.

Unstained slides will be prepared for macrodissection and nucleic acid extraction. After pathology review, macrodissection of demarcated tumor will be performed and nucleic acids will be extracted and distributed to the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) for analysis. Additional tissue remaining after creating unstained slides for IHC and nucleic acid extractions will be banked for long-term storage at ambient temperature. At the MoCha Genomics Lab, the steps will be:

- DNA library prepared for WES.
- RNA library prepared for RNA-Seq.
- Library quantitation using ddPCR for both WES and RNA-Seq

- Denaturing and clustering of DNA and RNA libraries for sequencing
- Sequencing of WES and RNA-Seq libraries
- Data analysis for WES and RNASeq

5.10.1.1 **Specimen Receipt and Processing at the** EET Biobank

Formalin-fixed tissue from pre-treatment and Week 4 time points will be collected. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank, and slides will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction. DNA (for WES) will be banked in a stock vial and RNA (for RNAseq) will be divided into 5 aliquots; all nucleic acids will be stored in a -80°C freezer until distribution for testing.

Additional FFPE tissue remaining after creating unstained slides for IHC and nucleic acid extractions will be banked for long-term storage at ambient temperature.

For patients who decline biopsy, archival FFPE (blocks or slides) will be collected and stored at the EET Biobank.

DNA will be extracted from blood in EDTA tubes collected at Baseline. DNA will be stored in a -80°C freezer until distribution for testing.

5.10.1.2 Handling of Specimens(s)

Please refer to Appendix G, Laboratory Manual for specimen handling details.

5.10.1.3 Shipping of Specimen(s)

Please refer to Appendix G, Laboratory Manual for specimen shipping details.

5.10.1.4 Site Performing Correlative Study
MoCha Laboratory, Frederick National Laboratory for Cancer Research (FNLCR)
Chris Karlovich
chris.karlovich@nih.gov

5.10.2 RNA sequencing in tumor biopsies

We seek to determine whether changes in gene expression can potentially serve as a biomarker of treatment response or resistance through serial assessment in patients with IDH1/2 mutant solid tumors treated with olaparib. RNA will be extracted from formalin-fixed tissue samples.

Unstained slides will be prepared for macrodissection and nucleic acid extraction. After pathology review, macrodissection of demarcated tumor will be performed and nucleic acids will be extracted and distributed to the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) for analysis. Additional tissue remaining after creating unstained slides for IHC and nucleic acid extractions will be banked for long-term storage at

ambient temperature. At the MoCha Genomics Lab, the steps will be:

- DNA library prepared for WES.
- RNA library prepared for RNA-Seq.
- Library quantitation using ddPCR for both WES and RNA-Seq
- Denaturing and clustering of DNA and RNA libraries for sequencing
- Sequencing of WES and RNA-Seq libraries
- Data analysis for WES and RNASeq

5.10.2.1 Specimen Receipt and Processing at the Biorepository

Formalin-fixed tissue obtained pre-treatment (or archival FFPE tissue) and Week 4 time points will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank, and slides will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction. DNA (for WES) will be banked in a stock vial and RNA (for RNAseq) will be divided into 5 aliquots; all nucleic acids will be stored in a -80°C freezer until distribution for testing.

Additional FFPE tissue remaining after creating unstained slides for IHC and nucleic acid extractions will be banked for long-term storage at ambient temperature.

5.10.2.2 Handling of Specimens(s)
Please refer to Appendix G, Laboratory Manual for specimen handling details.

5.10.2.3 Shipping of Specimen(s)
Please refer to Appendix G, Laboratory Manual for specimen shipping details.

5.10.2.4 Site Performing Correlative Study
MoCha Laboratory, Frederick National Laboratory for Cancer Research (FNLCR)
Chris Karlovich
chris.karlovich@nih.gov

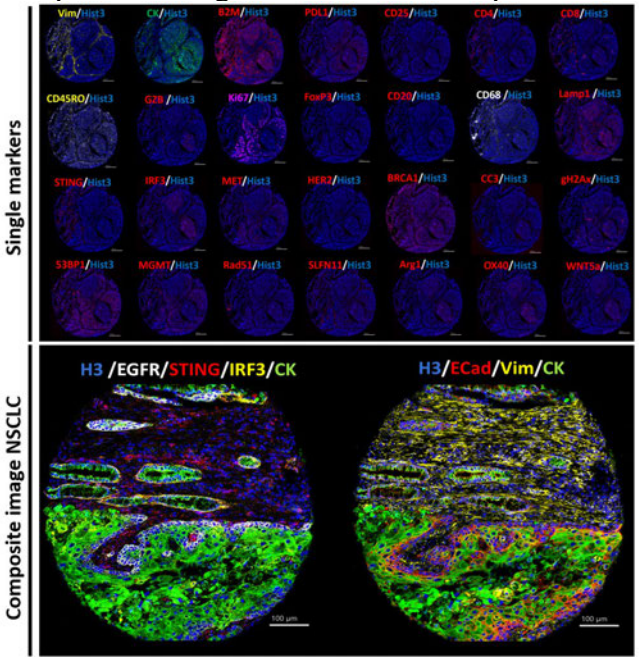
5.10.3 Multiplexed Quantitative Immunofluorescence (mQIF) and CyTOF – Imaging Mass Cytometry (IMC)

The goal of these studies is to evaluate the impact of IDH mutations, HRD and treatment with olaparib on tumor tissues. To address this, the Schalper laboratory will analyze intact paraffin-embedded tumor slides using state of the art quantitative protein analysis strategies. The laboratory will also take advantage of multiplexing protocols to accommodate numerous targets in each experimental run allowing the visualization of spatial interactions and maximizing the use of tumor specimens. The laboratory will also study the association between circulating markers and tumor features at different time points during treatment. The Schalper laboratory has validated protocols for systematic analysis of human specimens using mQIF and IMC panels.

Using spatially resolved mQIF assays, the Schalper laboratory will simultaneously map the levels of key DNA/HRD sensors, tumor-specific markers, mutant IDH proteins and stromal/immune cell components in conventional biopsy sections. Specifically, mQIF panels will include 4-6 individual markers such as DAPI for all nuclei, cytokeratin for tumor epithelial cells or GFAP for gliomas; γH2AX, RAD51, and/or mutant IDH1/2 proteins. Additional panels will be measured in consecutive tumor sections and include immune cell markers such as T/B-cell indicators (e.g. CD3, CD4, CD8, CD20). The markers will be measured in user defined compartments using multispectral imagers and analyzed using automated tissue and cell segmentation algorithms.

For the exploratory CyTOF/IMC studies, the Schalper laboratory will use previously validated metal-conjugated primary antibodies to analyze multiplexed panels for simultaneous detection of up to 35 individual markers in conventional tumor sections. The markers will include cancer and immune cell lineage indicators (Histone3, cytokeratin, ,Vimentin, E-cadherin, etc), DDR (gH2AX, RAD51, 53BP1, BRCA1, ATM, etc), major oncogenic drivers (EGFR, HER2, MET) and functional markers (Ki-67, GZB, LAMP1, etc) (see Figure below). They will be measured in selected tumor areas using the Hyperion/IMC instrument at Yale University. Data will be analysed using marker-assisted and visual tissue segmentation strategies with continuous marker scores as output. See image below for an example.

Yale-AZ DDR-IO IMC panel	
Marker	Metal tag
Histone 3	176Yb
Vimentin	143Nd
pan-CK	148Nd
E-cadherin	158Gd
Ki-67	168Er
HER2	141Pr
EGFR	142Nd
MET	167Er
γH2Ax	165Ho
RAD51	147Sm
53BP1	145Nd
BRCA1	172Yb
ATM	146Nd
SLFN11	144Nd
MLH1	171Yb
MGMT	160Gd
STING	166Er
cGAS	152Sm
IRF3	153Eu
BCL-XL	154Sm
cPARP	174Yb
CD4	156Gd
CD8	162Dy
CD20	161Dy
FOXP3	155Gd
CD45RO	149Sm
CD25	163Dy
OX40	170Er
GZB	173Yb
LAMP1	151Eu
CD68	159Tb
ARG1	164Dy
PD-L1	150Nd
β2M	169Tm



Analysis of continuous protein target levels using mQIF and CyTOF/IMC will be performed using correlation functions, non-parametric tests and Cox proportional hazards models for survival. Selected markers will also be binarized to study categorical associations; and integrated into multi-modal signatures using regressive models.

5.10.3.1 Collection of Specimen(s)

Please refer to Appendix G, Laboratory Manual for specimen collection details.

5.10.3.2 Handling of Specimens(s)

Formalin-fixed tissue obtained pre-treatment (or archival FFPE tissue) and Week 4 time points will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank. The Biorepository will create 10 5-micron unstained, unbaked, charged slides to distribute for analysis. Remaining tissue from the core used for multiplexed QIF and CyTOF analysis will be used for the Rad51 assay (Section 5.10.4).

Additional FFPE tissue remaining after creating unstained slides for IHC and nucleic acid extractions will be banked for long-term storage at ambient temperature.

5.10.3.3 Shipping of Specimen(s)

Please refer to Appendix G, Laboratory Manual for specimen shipping details.

5.10.3.4 Site Performing Correlative Study

Laboratory of Dr. Kurt A. Schalper
Yale School of Medicine

5.10.4 RAD51 focus formation assay

A crucial event during Homologous Recombination (HR)-mediated DNA repair is the formation of the RAD51 nucleofilament at sites of double-strand breaks. These structures appear as sub-nuclear foci when detected by a RAD51 specific antibody and the presence of such sub-nuclear RAD51 foci is a surrogate functional marker for HR status. In addition, HR-mediated DNA repair is restricted to cells in the S-phase of the cell cycle. Therefore, by staining for Geminin, a marker for cells in S-phase, and RAD51, it is possible to rapidly determine the functional status of HR in the sample.

To perform the RAD51 assay, at the Shapiro laboratory at the Dana-Farber Cancer Institute, two 5μm thick serial sections of a formalin fixed paraffin embedded sample will be independently stained using antibodies to Geminin and RAD51. Presence of Rad51 foci and Geminin positivity in tumor cells within the sample will be assessed. There must be more than 3 RAD51-foci in the nucleus to designate the tumor cell as RAD51-foci positive. Presence of at least one RAD51 foci positive tumor cell in a minimum of four 40X fields are required to indicate HR proficiency. If there are no RAD51 foci positive tumor cells and if greater than 3% of the tumor cells are Geminin positive, the sample is classified as HR-deficient. If there are no RAD51 foci positive tumor cells and if fewer than 3% of tumor cells are Geminin positive, then it is not possible to assign HR status since the fraction of S-phase cells are low.

5.10.4.1 Collection of Specimen(s)

Please refer to Appendix G, Laboratory Manual for specimen collection details.

5.10.4.2 Handling of Specimens(s)

Formalin-fixed tissue obtained pre-treatment (or archival FFPE tissue) and Week 4 time points will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank. Three (3) serially sectioned and numbered slides will be used for Rad51 analysis.

Additional FFPE tissue remaining after creating unstained slides for IHC and nucleic acid extractions will be banked for long-term storage at ambient temperature. The Biorepository will create two 5-micron unstained, unbaked, charged slides to distribute for analysis.

5.10.4.3 Shipping of Specimen(s)

Please refer to Appendix G, Laboratory Manual for specimen shipping details.

5.10.4.4 Site Performing Correlative Study

Laboratory of Dr. Geoffrey Shapiro
Dana Farber Cancer Institute

6. TREATMENT PLAN

6.1 Agent Administration

Patients will be treated with olaparib 300 mg q12hrs each day of a 28-day cycle in tablet formation and AZD6738 160 mg qday on days 1-7 of a 28-day cycle in tablet formation until disease progression, unacceptable toxicity, withdrawal of consent or death.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 2.3. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

For all centers, olaparib and AZD6738 tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib and AZD6738 will be dispensed to patients on Day 1 and every 28 days thereafter until the patient completes the study, withdraws from the study or closure of the study. Olaparib is available as a film-coated tablet containing 100mg or 150mg of olaparib. AZD6738 is available as round white coated tablets containing 20 or 80 mg of AZD6738.

Patients will be administered olaparib orally twice daily at 300 mg BID continually. 300mg olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

Patients will be administered AZD6738 orally once daily at 160 mg on days 1-7 of a 28-day cycle. AZD6738 tablets should be taken at the same time each day with one glass of water. The AZD6738 tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

When AZD6738 is administered in combination with olaparib, patients should fast for 2 hours before dosing and for 1 hour after dosing.

If vomiting occurs shortly after the olaparib or AZD6738 tablets are swallowed, the dose should only be replaced if all the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., because of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

The patient will be requested to maintain a medication diary of each dose of medication (See APPENDIX F). The medication diary will be returned to clinic staff at the end of each course.

6.1.1 CTEP IND Agent: Olaparib

Oral. Olaparib doses can be taken without regard to food. No routine premedications are required.

6.1.2 CTEP IND Agent: AZD6738

Oral. Do not eat or drink (except water only) for at least 2 hours prior to dosing and for at least 1 hour after dosing AZD6738 tablets. Do not crush, chew or split the tablets.

6.1.3 Other Modality(ies) or Procedures

N/A

6.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of olaparib and/or AZD6738 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Reason for use, dates of administration including start and end dates, and dosage information including dose and frequency will also be recorded in the CRF. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. APPENDIX B (Patient Drug Information Handout and Wallet Card) should be provided to patients.

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF).

6.2.1 Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication. Live virus and live bacterial vaccines should not be administered while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and

the effects with olaparib and/or AZD6738 are unknown.

Palliative radiotherapy

Palliative radiotherapy is not allowed during the study.

6.2.2 Restricted concomitant medications

6.2.2.1 Strong or Moderate CYP3A inhibitors and inducers

Strong or moderate CYP3A **inducers and inhibitors** should not be taken with Olaparib or AZD6738. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib and AZD6738. If a patient requires use of a strong or moderate CYP3A inducer or inhibitor after starting study treatment, then AZD6738 and olaparib should be discontinued and the patient must come off study treatment. If one drug is discontinued, both must be discontinued.

6.2.2.2 P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib and/or AZD6738. Caution should therefore be observed.

6.2.2.3 Effect of olaparib on other drugs

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.
Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.
The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.
Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 - furosemide, methotrexate

6.2.2.4 Effect of AZD6738 on other drugs

Based on limited in vitro data, AZD6738 may increase the exposure to substrates of BCRP, CYP3A4, CYP1A2, CYP2B6, OATP1B1, MATE1, MATE2K, OATP1B3, and P-gp.

Based on limited in vitro data, AZD6738 may reduce the exposure to substrates of CYP1A2, CYP2B6 and CYP3A4.

Examples of substrates include:

- BCRP – topotecan, rosuvastatin, sulfasalazine, diflomotecan, imatinib, atorvastatin, and methotrexate
- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- MATE1, MATE2K – metformin

6.2.2.5 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin, low molecular weight heparin and novel oral anticoagulants (NOACs) are permitted.

6.2.2.6 Anti-emetics/Anti-diarrheals

If a patient develops nausea, vomiting and/or diarrhea, these symptoms should be reported as AEs (see Section 7.4.2) and appropriate treatment should be administered.

6.2.2.7 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

6.2.2.8 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

6.2.2.9 Grapefruit juice

It is prohibited to consume grapefruit juice while on olaparib therapy.

6.2.3 Contraception

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (as described in APPENDIX E). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (as described in APPENDIX E).

Male patients must use a condom during treatment and for 6 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (as described in APPENDIX E) if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 6 months following the last dose of olaparib.

For details of acceptable methods of contraception refer to APPENDIX E, Acceptable Birth Control Methods.

6.3 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study. The patient is at any time free to discontinue treatment, without prejudice to further treatment. If a patient ceases taking either olaparib or AZD6738, either by choice or due to toxicities, he or she must cease taking the other agent and will no longer be on active treatment.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Severe patient non-compliance with the study protocol
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual

period) at any time during study participation.

- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.4 Duration of Follow Up

Patients will be followed for 30 days after removal from study or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, death, or any other discontinuation criteria, whichever comes first. Patients who start a new anti-cancer therapy in the absence of disease progression should continue to follow the protocol schedule until there is confirmed disease progression, withdrawal of consent, death, or any other discontinuation criteria, whichever occurs first.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 General Guidance

Any clinically significant and/or unacceptable toxicity observed during the course of the study should be managed in the first instance by interruption of the dose of study treatment, dose reductions if necessary and administration of supportive therapy.
If the toxicity resolves or reverts to ≤CTCAEv5 grade 1 or 2 (depending on the toxicity, see Table 1) treatment with ceralasertib and/or olaparib may be restarted using the rules in section 7.2 for dose modifications. Patients who have their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.
If the toxicity does not resolve to ≤ CTCAEv5 grade 1 or 2 (depending on the toxicity) or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity.
Repeat dose interruptions are allowed as required for a maximum of 28 days on each occasion as recommended in Table 1. If the duration of ceralasertib or olaparib dose interruption is longer than 28 days, the case should be discussed with the Principal Investigator.

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 28 days for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Study Physician.
Study treatment should be stopped at least 3 days prior to planned surgery and restarted 10 days post-surgery if the wound has healed. If the wound has not healed well, a further 14 days may be allowed and the patient can recommence ceralasertib if there is no evidence of disease progression based on the clinical judgement. No stoppage of study treatment is required for any biopsy procedure. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

The dose of ceralasertib and olaparib must not be adjusted under any other circumstances unless prior agreement is given by the Sponsor.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the CRF.

7.2 Guidance for Dose Modification and Interruption

Refer to Table 1, Table 2 and Table 3 for dose modification and stopping criteria for ceralasertib and olaparib.

Please note that for simultaneous toxicities (for example, anaemia and neutropenia), the event should be considered singular and no further dose modification should be made providing that both toxicities resolve within 28 days. However, sequential toxicities (for example, anaemia followed by neutropenia) should follow the guidance below; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle. Once dose is reduced, escalation is not permitted.

Table 1. Dose interruption and stopping criteria for ceralasertib and olaparib

Event	Action
Grade 1 neutropenia and/or thrombocytopenia	Ceralasertib and olaparib dosing may continue if neutrophil count is ≥ 1500/mm^3 and/or platelet count is ≥75,000/mm^3
Grade 1-2 toxicities (except neutropenia and thrombocytopenia)	Investigator decision whether to interrupt ceralasertib and/or olaparib (max 28 days) or continue treatment. Treatment may be resumed at the same dose level prior to interruption.
Grade 2 neutropenia or Grade 3 anaemia	Interrupt ceralasertib and olaparib (max 28 days) and give appropriate supportive treatment e.g. transfusion, until AE improves to at least neutrophil count ≥1500/mm^3 and haemoglobin ≥8.0 g/dL, then restart reducing the dose of ceralasertib by 1 level.
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt ceralasertib only (max 28 days) and give appropriate supportive treatment until platelets improve to at least ≥100,000/mm3. At resolution, it is not mandatory to lower the dose as blood counts may recover during the "off period" on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, ceralasertib should be restarted with a dose reduction by 1 level for ceralasertib. **Subsequent occurrences** Interrupt ceralasertib only (max 28 days) and give appropriate supportive treatment. Treatment may be restarted with a reduced dose of ceralasertib when the toxicity is resolved or investigator discretion to stop treatment.
Grade 4 thrombocytopenia	Interrupt ceralasertib and olaparib (max 28 days) and give appropriate supportive treatment; investigator discretion on whether to restart treatment with a dose reduction by 1 dose level for both drugs or stop treatment when the platelet count has recovered to ≥100,000/mm3.
Grade 3-4 toxicity (except grade 3 anaemia and grade 3-4 thrombocytopenia)	**First occurrence** Interrupt ceralasertib and /or olaparib (max. 28 days) and given appropriate supportive treatment; restart treatment with a dose reduction by 1 level for ceralasertib and/or olaparib when the toxicity is resolved (grade ≤1 or 2 depending on the toxicity or returns to baseline).

	Subsequent occurrences Interrupt ceralasertib and /or olaparib (max 28 days) and give appropriate supportive treatment. Investigator discretion whether to restart treatment with a reduced dose of ceralasertib and/or olaparib or to stop treatment.
Vomiting	If vomiting occurs shortly after ceralasertib is swallowed, the dose should only be replaced if all of the intact capsules can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken, and patient should continue with next dose at allotted time.

Table 2. Dose reduction levels for ceralasertib

Initial dose	160 mg OD days 1–7
Level 1 dose reduction	120 mg OD days 1–7
Level 2 dose reduction	80 mg OD days 1–7
Level 3 dose reduction	Stop treatment

Table 3. Dose reduction levels for olaparib

Initial dose	300 mg twice daily
Level 1 dose reduction	250 mg twice daily
Level 2 dose reduction	200 mg twice daily
Level 3 dose reduction	Stop treatment

7.3 Management of Prolonged Hematological Toxicities

If a patient develops **prolonged hematological toxicity** such as:

- ≥2 week interruption or delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes and peripheral blood smear should be performed. Study treatment should be discontinued if blood counts do not recover to CTC Grade 1 or better within 4 weeks of dose interruption.
If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to

standard hematological practice.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as detailed in Section 10.6. Study treatment should be discontinued if diagnosis of MDS and/or AML is confirmed.

7.4 Individual Stopping Criteria

Hepatic
ALT or AST or ALP* > 5 x ULN
ALT or AST or ALP* > 3 x ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (>5%)
[ALT or AST > 3 x ULN] and [total bilirubin > 2 x ULN or INR^{+} > 1.5 or other evidence of impairment to the synthesis function of the liver]
* In the presence of bone mets assess bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver)
$^{+}$ Unless patient is receiving warfarin
Please refer to Appendix C "Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law."

Cardiovascular
Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes.
Symptomatic orthostatic fall in systolic blood pressure of more than 20 mmHg compared to resting supine systolic blood pressure.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agents

8.1.1 Olaparib (NSC# *747856*)

Chemical Name: 4-[(3-[[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl]-4-fluorophenyl)methyl]phthalazin-1(2H)-one

Other Names: AZD2281; KU-0059436; CO-CE 42

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

Molecular Formula: C24H23FN4O3 M.W.: 434.46

Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range

Mode of Action: Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5' diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

Description: crystalline solid

How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib in 100 mg and 150 mg strengths.

- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg are 14.5 mm x 7.25 mm oval-shaped

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

Storage: Store in a secure location below 30° C (86° F).

If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to room temperature 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: Shelf-life studies are ongoing. Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

Route and Method of Administration: Oral. Take tablets without regard to meals. When AZD6738 is administered in combination with olaparib, patients should fast for 2 hours before dosing and for 1 hour after dosing.

Potential Drug Interactions: In vivo data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant

administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro data shows olaparib is a substrate for P-glycoprotein (P-gp), but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), organic cation transporter 1 (OCT1), multi-drug resistance protein 2 (MRP-2) efflux transporter or breast cancer resistance protein (BCRP). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

Based on in vitro data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4 and potentially induces CYP 2C9, 2C19 and P-gp. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. In vitro studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least six (6) months after the last dose of olaparib. Male study participants should avoid fathering a child or donating sperm during the study and for six (6) months after the last dose of olaparib. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery.

Olaparib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Olaparib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.3)

8.1.2 AZD6738 (NSC #802785)

Chemical Name: Imino-methyl-[1-[6-[(3R)-3-methylmorpholin-4-yl]-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl]cyclopropyl]-oxo-λ6-sulfane

Other Names: AZ13386215

CAS registry number: 1352226-88-0

Classification: Ataxia Telangiectasia and Rad3-Related (ATR) protein kinase inhibitor

Molecular Formula: $C_{20}H_{24}N_6O_2S$

Molecular Weight: 412.51 g/mol

Approximate Solubility: AZD6738 free base solubility is >100 mg/mL in Simulated Gastric Fluid (pH 1.6) and 0.76 mg/mL in Fasted State Simulated Intestinal Fluid (pH 6.5)

Mode of Action: AZD6738 is a potent, selective inhibitor of the ATR protein, which is recruited to stalled DNA replication forks during DNA damage. ATR activation leads to cell cycle arrest in the S phase while DNA is repaired, and the stalled replication fork is resolved. ATR inhibition leads to the inability to resolve stalled replication forks, the accumulation of DNA damage and subsequent rapid cell death.

Description: AZD6738 is a crystalline powder.

How Supplied: AstraZeneca supplies and PMB, DCTD, NCI distributes AZD6738 as 20 mg and 80 mg film-coated tablets. Each tablet contains a blend of AZD6738, mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and silicon dioxide. The coating is Opadry® II white. Tablets are available in induction-sealed HDPE bottles as described:

20 mg: 6-mm round, white tablets packaged in 24-count bottles
80 mg: 11-mm round, white tablets packaged in 16-count bottles

Storage: Store AZD6738 tablets <30°C. Do not freeze.

If a storage temperature excursion is identified, promptly return AZD6738 to <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. The manufacturer does not have stability data to support repackaging tablets. Dispense tablets in the original container.

Route and Method of Administration: Oral. Do not eat or drink (except water only) for at least 2 hours prior to dosing and for at least 1 hour after dosing AZD6738 tablets. Do not crush, chew or split the tablets.
If vomiting occurs shortly after AZD6738 is swallowed, the dose should only be replaced if all of the intact tablets can be counted and then treatment resumed with the following scheduled dose. The scheduled dose can be taken up to 2 hours after the scheduled dose

time. If greater than 2 hours, the missed dose should not be taken and patient should continue with next dose at the scheduled time.

Potential drug interactions: AZD6738 is primarily metabolized by CYP3A4, with lesser contribution by CYP 2C8, 2C9, 2C19 and 3A5. CYP 1A2, 2A6, 2B6, 2D6 and 2E1 were not shown to metabolize AZD6738 in vitro. Avoid co-administration of strong CYP3A4 inducers and inhibitors. Advise patients not to consume grapefruit, grapefruit juice or Seville oranges (including marmalade, juice, etc) while participating in the study. Refer to the protocol document for additional guidance.

AZD6738 is a substrate of P-gp and BCRP and a likely substrate of OATP1B1 and/or OATP1B3 transporter systems. Avoid co-administration of strong inhibitors or inducers of P-gp or BCRP. Refer to the protocol document for additional guidance.

AZD6738 has the potential to inhibit P-gp, BCRP, OATP1B1, OATP1B3, MATE1 and MATE2K protein transporter systems. It did not show inhibition of OAT1, OAT3 or OCT2 during in vitro studies. Use caution with co-administration of substrates of these transporter systems since their drug exposures may be increased. In vitro studies demonstrate that AZD6738 does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2B6, CYP2C8, and CYP3A4/5.

In vitro studies show that AZD6738 has a low potential to induce CYP1A2, CYP2B6 and CYP3A4. Use caution with co-administration of substrates that are either completely metabolized by these enzymes or substrates with a narrow therapeutic index since their drug exposures may be decreased.

Patient care implications: Advise women of child-bearing potential to use two (2) highly effective forms of contraception while receiving study treatment and for 1 (one) month after the last dose.

Advise men who are sexually active to use barrier contraception while receiving study treatment and for one (1) week after the last dose. Male study participants must use barrier contraception while receiving study treatment and for 6 (six) months after the last dose if the female partner is pregnant. Female partners of male study participants should use a highly effective form of contraception for 6 (six) months after the last dose.

Advise patients to avoid excessive sun exposure while receiving AZD6738.

AZD6738 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

AZD6738 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.3).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 **NCI-supplied agents may be requested** by eligible participating Investigators (or their authorized designee) at each participating institution. 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 participating investigator at that institution.

Submit agent requests 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. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Sites can order study agents in OAOP when a patient is enrolled to treatment. Agent orders can be expedited overnight Monday-Thursday when sites provide expedited courier information.

8.1.3.2 **Agent Inventory Records:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP 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 via email.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/

- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. STATISTICAL CONSIDERATIONS

The cholangiocarcinoma cohort has closed to accrual. Protocol amendment version 08/22/2022 reflects this closure.

9.1 Primary objective

The primary objective of this phase II study is to determine the objective response rate (ORR) in subjects with recurrent/progressive IDH1/2-mutant solid tumors. Previous experiences suggest that response rate for this type of solid malignancies is approximately 20%.

9.2 Baseline data analysis

Demographic information such as age and race will be tabulated. Descriptive statistics, including means, medians, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, will be presented.

9.3 Analysis of primary endpoint

The effectiveness of the new combination in patients for each cohort will be independently assessed by objective response rate (ORR). The exact two-sided 95% confidence intervals for the ORR will be reported.

9.4 Toxicity evaluation

Toxicities will be evaluated utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0, available at https://ctep.cancer.gov). Adverse medical events will be tabulated. NCI toxicity Grade 3 and Grade 4 laboratory abnormalities will be listed. Reporting of adverse events is described in Sections 10.3 and 10.4. All patients who receive any amount of study drugs will be evaluable for toxicity.

An early review will be made of safety in the initial 10 patients treated on each arm. If unacceptable toxicity (defined below) occurs in 3 of these initial 10 patients enrolled on either arm, a dose de-escalation of olaparib will occur for all patients currently enrolled and any who enroll thereafter (250 mg PO bid continuously). After the 10th patient, we will delay treatment on the combination arm until the 10th patient has been assessed for 4 weeks (28 day cycle).

After the 10th patient is treated, the initial safety review will occur to obtain consensus from the participating physicians on how to proceed. If there are physicians participating in the study who are not able to be available for this discussion, we will send them the relevant information and ask them to respond regarding their assessment of the safety of this dosing regimen.

Unacceptable toxicity will include any of the following adverse events related to drug:
1.) Grade 4 myelosuppression over 7 days
2.) Grade 4 Febrile neutropenia
3.) Grade 4 thrombocytopenia
4.) Thrombocytopenia with associated excessive bleeding
5.) Grade 3 uncontrolled diarrhea despite anti-diarrheals
6.) Grade 3 nausea and/or vomiting despite the use of anti-emetics
7.) Any other uncontrolled grade 3 toxicity (other than alopecia)
Note: Hypothyroidism requiring thyroid supplementation or decreased adrenal or pituitary function requiring steroid replacement would not necessitate de-escalation.

9.5 Sample Size/Accrual Rate

A two-stage MinMax design described by Simon will ensure that the number of the total patients exposed to this therapy is minimized. If there is evidence that the true underlying objective response rate (ORR) is at least improved by 25% when comparing with the historical control data, consideration will be given for further testing of the new combination. However, if the new combination is inactive, then the trial should be terminated early. Initially, 14 eligible patients will be entered into each of two arms in the study. If there are fewer than 4 responses in these first 14 patients, that arm will be terminated with the conclusion that there is little evidence to suggest that the overall response rate would reach 45%, i.e., a 20% ORR improvement (45% vs. historical control ORR = 20%), If there are four or more responses in these first 14 patients, that arm of the trial will continue until 25 patients have been treated. If there are fewer than 8 responses in these 25 patients then that arm of the trial will be terminated. This design provides 90% statistical power to detect a difference of 25% (45% vs. 20%) with a significance level less than 0.10 (type I error). Therefore, a total of 50 patients (25 per cohort) will ensure each cohort has sufficient statistical power.

The total estimated monthly accrual is 2 patients enrolled per month, so accrual should take approximately 24 months, with a follow up period of 1 year.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Asian	2	2	0	0	**4**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	3	3	0	0	**6**
White	14	16	3	3	**36**
More Than One Race	1	1	1	1	**4**
Total	**20**	**22**	**4**	**4**	**50**

9.6 Stratification Factors

There are no stratification factors.

9.7 Analysis of Secondary Endpoints

For lifetime data analyses, e.g., overall and progression free survival and duration of response, the study survival will be estimated using the Kaplan-Meier method with the 95% confidence intervals (CIs). The CI based on the Greenwoods variance will be reported. In addition, the possible risk factors will be compared for survival with log-rank test. For multivariate analysis, the proportional hazards Cox model will be applied to investigate potential prognostic factors, such as age and stage of disease on the survival data. The adjusted p-values of the odds ratios and the adjusted 95% confidence interval will be reported.

9.8 Analysis of Exploratory Endpoints

Absolute and fold changes for γH2AX foci will be calculated between baseline and subsequent follow-up (pre-treatment and on-treatment biopsies). These will be displayed graphically vs. time for each cohort. Differences will be plotted vs. response status. Wilcoxon sign-rank test as well as paired t-tests will be used to evaluate if differences between baseline and each subsequent time point are significant. Summary statistics will be reported (with 95% confidence intervals) to demonstrate mean differences in fold-change (or log fold-change) between responders and non-responders. 2HG levels in tumor and plasma will be compared to treatment responses. The Mann-Whitney U test will be used to test for differences in post-treatment tissue and plasma 2HG

concentrations between patients with a response to treatment and those without. We will also apply analysis of covariance (ANCOVA) for post-treatment plasma concentration in 2HG adjusted for the pre-treatment plasma concentration between patients with a response to treatment and those without. Differences with $p \leq 0.05$ will be considered statistically significant. The area under the receiver operating characteristic curve (ROC AUC) will be calculated to determine the cutoff value of the 2HG difference. The optimal cutoff value will be determined at the point on the ROC curve at (sensitivity + specificity − 1) is maximized (Youden index).

The primary objective of these biopsies is for the exploratory analysis. The proposed minimum of 10 biopsy samples per arm for the first stage provides 90% power to detect an effect size of 1.5 with un-adjusted two-sided type I error = 5%. The effect size is defined as ratio of mean difference between two arms to the standard deviation.

9.9 Reporting and Exclusions

9.9.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with AZD6738 and olaparib.

9.9.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. The only exception to this rule is if a patient is found to be ineligible for the study.

Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) should be included in the main analysis of the response rate. However, if a patient’s tissue is not confirmed centrally to have an eligible IDH1/2 mutation, that patient will not be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

Patients with previously identified IDH1/2 mutation in a CLIA certified laboratory are eligible, but the mutation must be verified later in the central laboratory. If IDH mutation fails to confirm those patients will be excluded from the final analysis.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

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.

10.1.1 CAEPRs for CTEP IND Agents

10.1.1.1 CAEPR for Olaparib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Olaparib (AZD2281, NSC 747856)

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 3449 patients.* Below is the CAEPR for Olaparib (AZD2281).

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

Version 2.6 June 5, 2023[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
Abdominal pain			***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
	Urinary tract infection		
INVESTIGATIONS			
	Creatinine increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	
VASCULAR DISORDERS			
		Vascular disorders - Other (venous thromboembolism)	

NOTE: New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[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.

Adverse events reported on Olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever; Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain

NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus
VASCULAR DISORDERS - Arterial thromboembolism; Flushing; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

Note: Olaparib (AZD2281) 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.

10.1.1.2 CAEPR for AZD6738

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
AZD6738 (ceralasertib, NSC 802785)

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 179 patients.* Below is the CAEPR for AZD6738 (ceralasertib).

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

Version 2.1, February 27, 2025[1]

Adverse Events with Possible Relationship to AZD6738 (ceralasertib) (CTCAE 5.0 Term) [n= 179]			**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			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Dyspepsia		
Nausea			***Nausea (Gr 2)***

Adverse Events with Possible Relationship to AZD6738 (ceralasertib) (CTCAE 5.0 Term) [n= 179]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (COVID-19)		
	Lung infection		
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Headache		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		***Dyspnea (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		***Rash maculo-papular (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]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.

Adverse events reported on AZD6738 (ceralasertib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD6738 (ceralasertib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (bone marrow failure); Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (splenic rupture); Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Pericardial effusion
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Colonic obstruction; Dysphagia;

Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage)[2]; Mucositis oral; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Disease progression; Fever; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (drug-induced liver injury); Hepatobiliary disorders - Other (biliary obstruction); Hepatobiliary disorders - Other (cholangitis)
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (hypogammaglobulinemia)
INFECTIONS AND INFESTATIONS - Abdominal infection; Hepatitis viral; Herpes simplex reactivation; Infections and infestations - Other (diarrhea infectious); Infections and infestations - Other (gastroenteritis); Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CD4 lymphocytes decreased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Investigations - Other (elevated C-reactive protein); Lymphocyte count decreased; Lymphocyte count increased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Peripheral sensory neuropathy; Stroke
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (acute renal insufficiency)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (prostatitis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Epistaxis; Hypoxia; Oropharyngeal pain; Pleural effusion; Pneumonitis; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Photosensitivity; Pruritus; Skin ulceration
VASCULAR DISORDERS - Hypotension; Superior vena cava syndrome; Thromboembolic event; Vascular disorders - Other (thrombophlebitis)

Note: AZD6738 (ceralasertib) 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.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 10.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AEs) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

10.3.4 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL SAEs</u> that meet the above criteria **<u>MUST</u>** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

<u>Expedited AE reporting timeframes are defined as:</u>

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

10.3.5 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anemia	2	No
GASTROINTESTINAL DISORDERS	Abdominal pain	2	No
GASTROINTESTINAL DISORDERS	Constipation	2	No
GASTROINTESTINAL DISORDERS	Diarrhea	2	No
GASTROINTESTINAL DISORDERS	Dyspepsia	2	No
GASTROINTESTINAL DISORDERS	Nausea	2	No
GASTROINTESTINAL DISORDERS	Vomiting	2	No
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	2	No
METABOLISM AND NUTRITION DISORDERS	Anorexia	2	No
NERVOUS SYSTEM DISORDERS	Headache	2	No
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea	2	No

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported**

expeditiously through CTEP-AERS must also be reported in routine study data submissions.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.4.1 Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

10.4.2 Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated determination (eg, laboratory values, vital signs) should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.
If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s s).
Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.
Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to APPENDIX C 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

10.4.3 Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.4.4 Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used,

there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

10.4.5 Overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established. Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg twice daily (tablet).
Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

10.4.6 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to Study PI within the usual timeframes.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

10.8 Olaparib adverse events of special interest

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to Study Principal Investigator. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to Study Principal Investigator whether it is considered a non-serious AE [eg non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

11. STUDY CALENDAR

Unless otherwise indicated, screening evaluations are to be conducted within 28 days prior to start of protocol therapy. Cycle 1 Day 1 ECG and laboratory results must be reconfirmed and remain within eligibility parameters as per section 3 for patient to be dosed. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Biopsy procedures will occur at pre-treatment (biopsy within 2 weeks of starting therapy) and after 1 cycle of treatment (4 weeks), with the latter occurring only as long as the patient has received a minimum of 1 Cycle of treatment following the second biopsy procedure (or 21 of 28 days given the +/- 7 day allowable window for the on treatment biopsy). Each biopsy will consist of 6 passes of a large gauge needle (such as 16 or 18g) for core biopsy. Unless otherwise indicated, there is a +/- 4 day window for all visits and assessments.

	Screening (Day – 28 to Day 1)[A]	D1 Cycle ≥ 1	C1D8	C1D15	4 weeks	C2D8	C2D15	8 weeks	Every 8 weeks	Off study[B]	Follow Up	Long term Follow Up
Olaparib[Q]		X----------X										
AZD6738[R]		X----------X										
Informed consent	X											
Inclusion/Exclusion Criteria	X											
Pregnancy Test[C]	X	X									X	
Molecular Selection of Patients based on Archival Tumor Tissue determined in a CLIA certified laboratory[D]	X											
Medical History	X											
Physical examination, including neurological examination[E]	X	X	X	X		X	X	X		X	X	
Weight	X	X						X				
Vital signs[F]	X	X	X	X		X	X	X		X		
ECOG Performance Status	X	X						X		X	X	
Hematology[G]	X	X[S]	X	X		X	X			X		
Chemistry[H]	X	X[S]	X	X		X	X			X		
Urinalysis[I]	X	If clinically indicated										
Coagulation[J]	X	If clinically indicated, except for patients on Warfarin										
Bone marrow or blood cytogenetic analysis[K]		If clinically indicated										
Concomitant medications	X	X	X	X			X			X		
Dosing compliance		X								X		
Adverse events	X	X	X	X			X			X	X	
Tumor Assessments[L]	X							X[L]	X[L]	X	X	
2HG plasma concentration[M]	X							X[M]	X[M]	X[M]		
2HG tumor tissue[N] concentrations	X				X[N]							
ECG[O]	X	X										
Biopsy[P]	X				X							
Whole blood in EDTA	X											
Anti-cancer therapy follow-up												X

A Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

B All patients with clinically significant abnormal laboratory results at treatment completion or study drug discontinuation visit are to be followed until the results return to normal (or patient's baseline), or until a valid reason, other than a drug- related effect, is identified. Patients with an unresolved AE or SAE event at treatment completion or study drug discontinuation will be contacted by the investigator or his or her designee to determine the status of the event until the event is resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the event**.**

C Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment and at each subsequent visit during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

D Subjects must have biopsy-confirmed evidence of an IDH1 or IDH2 mutation associated with neomorphic activity of the encoded proteins. See Section 2.4.1

for additional information on IDH1/2 mutation confirmation and those that are considered to be neomorphic.
E A complete physical examination will be performed at the following timepoints: Screening Visit, Day 1 Every Cycle, Discontinuation Visit, Follow-up Visit. Constitutional symptoms will be collected during screening and pre-dose at all other visits. Constitutional symptoms will include the presence/absence of pruritus, night sweats, recurrent fever ≥38.0ºC, fatigue, weakness and nocturia (a history of weight loss is to be collected at screening visit only).
F Vital signs (heart rate, systolic and diastolic blood pressure, oxygen saturation (pulse oximetry), respiration rate, weight, height (at screening) and temperature). At screening, vital signs should include postural blood pressure; this should be performed at subsequent visits if clinically indicated.
G Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials.
H Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]).
I Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required**.**
J Coagulation [activated partial thromboblastin time (APTT) and international normalized ratio (INR)] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.
K Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for patients with prolonged hematological toxicities. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to the Sponsor for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database**.** Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities.
L Patients will be evaluated until objective disease progression by RECIST 1.1. If a chest CT scan at baseline (screening CT will be the baseline scan) is not performed as part of the RECIST assessment, the patient should undergo a chest CT scan in order to document the lung parenchyma status at baseline. High resolution CT should be performed if clinically indicated by pulmonary symptoms any time during the study. For any new respiratory symptoms (cough, dyspnea, lower respiratory infection) not clearly explained by other factors (eg, dyspnea associated with substantial drop in hemoglobin), patients should have oxygen saturation measured. If <92%, the high resolution CT scan of the chest should be repeated and pulmonary function tests should be performed. Scans will be performed every 8 weeks (± 1 week) and it will continue until disease progression, consent withdrawal, or death, whichever occurs first. After 12 months, patients will undergo tumor assessments every 12 weeks (+/- 1 week) until confirmed disease progression. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, or death, whichever occurs first. If partial response (PR) or complete response (CR) is documented, a confirmatory scan will be performed 4 weeks later for PR/CR (whichever occurs first).
M. The concentrations of 2HG will be determined in patient plasma. Blood samples will be collected at screening/pre-treatment (Days -14 to -1), on day 1 of cycles 2, 4 and 8 and at time of confirmed disease progression per study schema (plasma only; -/+ 4 days). Sample handling instructions can be found in Section 5.2.1 and Section 5.3.1.
N. The concentrations of 2HG will be determined in patient tumor samples. FFPE samples will be accepted for analysis if a biopsy is not obtainable or the patient declines biopsy. On treatment biopsy will occur on C2D1, +/- 7 days. Sample handling instructions can be found in Appendix G, Laboratory Manual
O. ECGs are required within 28 days prior to starting study treatment in triplicate performed 2-5 minutes apart; on Day 1 of each cycle; and when clinically indicated. Cycle 1 Day 1 ECG results must be reconfirmed and remain within eligibility parameters as per section 3 for patient to be dosed.
P. Biopsy procedures to occur at pre-treatment (biopsy within 2 weeks of starting therapy, Days -14 to -1) and after 1 cycle of treatment (4 weeks, +/- 7 days), as long as the patient has received a minimum of 1 Cycle of treatment. Each biopsy will consist of 6 passes of a large gauge needle (such as 16 or 18g) for core biopsy.
Q. Olaparib: 300 mg orally BID continuously in 28-day cycles.
R. AZD6738: 160 mg orally once daily on days 1-7 of a 28-day cycle.
S. Cycle 1 Day 1 laboratory results must be reconfirmed and remain within eligibility parameters as per section 3 for patient to be dosed.

11.1 Study procedures

11.1.1 Laboratory safety assessment

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials. Coagulation [activated partial thromboblastin time (APTT) and international normalised ratio (INR)] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, fasting glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]) should be performed at each visit and when clinically indicated.

Urinalysis by dipstick should be performed at baseline [measuring hemoglobin, erythrocytes, blood, protein, albumin, and glucose] and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 7.3.4.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to APPENDIX C, 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions

11.1.2 Physical examination

A complete physical examination will be performed at the following timepoints: Screening visit, Day 1 every cycle, Discontinuation visit, Follow-up visit. Constitutional symptoms will be collected during screening and pre-dose at all other visits. Constitutional symptoms will include the presence/absence of pruritus, night sweats, recurrent fever ≥38.0ºC, fatigue, weakness and nocturia (a history of weight loss is to be collected at screening visit only). All adverse events should be recorded as explained in Section 10.4.

11.1.3 Resting 12 lead EKG

ECGs are required within 28 days prior to starting study treatment in triplicate performed 2-5 minutes apart; on Day 1 of each cycle; and when clinically indicated. Cycle 1 Day 1 ECG results must be reconfirmed and remain within eligibility parameters as per section 3 for patient to be dosed.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

11.1.4 Vital signs

11.1.4.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using a manual or automated blood pressure cuff after 5 minutes rest on a bed. For timings of assessments refer to Study Calendar

11.1.4.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan and Time Schedule.

11.1.4.3 Respiration rate

Respiration rate will be measured in breaths per minute and it will be measured while patient is at rest.

11.1.4.4 Weight

Weight will be measured in Kg.

11.1.4.5 Height

Height will be measured in cm.

11.1.5 Other safety assessments

11.1.5.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment and at each subsequent visit during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in

the patient's medical records.

11.1.5.2 Bone marrow or blood cytogenetic analysis

Bone marrow or blood cytogenetic analysis may be collected for patients with prolonged hematological toxicities as defined in Section 7.3.4. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database. These data are not required to be entered into CRF.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response. After 12 months, patients will undergo tumor assessments every 12 weeks until confirmed disease progression.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AZD6738 and olaparib.

Evaluable for objective response. All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. If a patient's tissue is not confirmed centrally to have an eligible IDH1/2 mutation, that patient will not be included in the main analysis of the response rate.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall

disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Patients who are lost to follow-up or who have not progressed or deveoped recurrent disease by the criteria above at the time of data cut-off will be censored for duration of response analysis at the time of their last study visit.

12.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Patients who are lost to follow-up or who have not progressed at the time of data cut-off will be censored for PFS analysis at the time of their last study visit.

12.1.7 Overall Survival

Overall survival (OS) is defined as the duration of time from start of treatment to time of death. Patients who are lost to follow-up or who have not died at the time of data cut-off will be censored for OS analysis at the time of their last study visit.

12.1.8 Response Review

Central confirmatory radiology review for best radiographic response will be performed by the Tumor Imaging Metrics Core (TIMC) at the Yale Cancer Center for patients treated at Yale. In the instance of a disagreement between a treating physician and the TIMC, the investigator will make the final decision as to whether a patient may continue on trial. At the study's conclusion, TIMC assessments will stand as the final

determination of a patient's response to therapy. We encourage other participating sites to use their TIMC or equivalent.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users), and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type,
- Rave Investigator role, must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR), and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

13.2.1 Responsibility for Data Submission

Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data

integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall

be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

   5. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Col
   6. laborator(s) for advisory review and comment prior to submission for publication.

Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B 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 drugs, **olaparib** and **AZD6738**. 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:

Olaparib interacts with a specific enzyme in your liver.

- The enzyme(s) in question is **CYP3A**, and olaparib is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.
- Based on limited in vitro data, **olaparib** may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It also may reduce reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

AZD6738 interacts with certain specific enzymes in your liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4/5, 1A2 and 2B6. AZD6738 is broken down by CYP3A4/5 and may be affected by other drugs that inhibit or induce these enzymes. AZD6738 induces CYP1A2, 2B6 and 3A4 which may affect the levels of other drugs that are dependent on these enzymes to be broken down and cleared from the body.
- Based on limited in vitro data, AZD6738 may increase the exposure to substrates of BCRP, CYP3A4, CYP1A2, CYP2B6, OATP1B1, MATE1, MATE2K, OATP1B3, and P-gp. Based on limited in vitro data, AZD6738 may reduce the exposure to substrates of CYP1A2, CYP2B6 and CYP3A4.
- The proteins in question are P-gp, BCRP, OATP1B1, OATP1B3, MATE1 and MATE2K. AZD6738 is dependent on P-gp and BCRP protein transporters to be moved in and out of cells/organs. AZD7638 may reduce the ability of other drugs to be moved in and out of cells/organs by inhibiting P-gp, BCRP, OATP1B1, OATP1B3, MATE1 and MATE2K protein transporters.

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

Olaparib and **AZD6738** 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:

Olaparib and **AZD6738** must be used very carefully with other medicines that use certain ***liver enzymes to be cleared from your system*.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **strong inducers/inhibitors of CYP3A4/5; sensitive substrates of CYP 1A2, 2B6 or 3A4; strong inhibitors/inducers of P-gp or BCRP protein transporters; sensitive substrates of P-gp, BCRP, OATP1B1, OATP1B3, MATE1 or MATE2K protein transporters.**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit, grapefruit juice or Seville oranges (including marmalade, juice, etc.) while participating in the study.
- Avoid excessive sun exposure while on study.
- 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 drugs **olaparib** and **AZD6738.** This clinical trial is sponsored by the NCI. **Olaparib** and **AZD6738** 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.

Olaparib interacts with a ***specific liver enzyme called CYP3A***, and **AZD6738** interacts with ***specific liver enzymes called CYP3A4/5, 1A2, 2B6 and transport proteins P-gp, BCRP, OATP1B1, OATP1B3, MATE1 and MATE2K***. They must be used very carefully with other medicines that interact with these enzymes and transporters.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP3A4/5; sensitive substrates of CYP 1A2, 2B6 or 3A4; strong inhibitors/inducers of P-gp or BCRP protein transporters; sensitive substrates of P-gp, BCRP, OATP1B1, OATP1B3, MATE1 or MATE2K protein transporters."
- 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 _____.

APPENDIX C ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE (AT) AND TOTAL BILIRUBIN (TBL) – HY'S LAW

Briefly, Hy's Law cases have the following three components:

The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo

Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)

No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe drug induced liver injury (DILI) when given to a larger population.

The following actions are required in cases of combined increase of aminotransferase and total bilirubin:

1. Confirmation

In general, an increase of serum AST/ALT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious. Of greater concern, delay in retesting may allow progression to severe worsening if the initial abnormality was the herald of a severe reaction to follow. The need for prompt repeat testing is especially great if AST/ALT is much greater than 3xULN and/or TBL is greater than 2xULN. For outpatient trials, or trials in which subjects are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AST/ALT >3xULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening. If close monitoring is not possible, the drug should be discontinued.

2. Close Observation

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels greater than 3xULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database.
Close observation includes:

Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
Obtaining a more detailed history of symptoms and prior or concurrent diseases.
Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
Obtaining a history of exposure to environmental chemical agents.
Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
Considering gastroenterology or hepatology consultations.

3. Decision to Stop Drug Administration

It has been observed that de-challenge (stopping drug administration) does not always result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity).

Promptly stopping the offending drug usually is the only potentially effective therapy.

Because transient fluctuations of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, continuing drug appears unacceptably dangerous if there is marked serum aminotransferase elevation or evidence of functional impairment, as indicated by rising bilirubin or INR, which represent substantial liver injury. Although there is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision will be affected by information on related drugs, the

accumulating clinical experience, the clinical status of the patient, and many other factors, the following can be considered a basic guide. Discontinuation of treatment should be considered if:

ALT or AST >8xULN
ALT or AST >5xULN for more than 2 weeks
ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It should be noted that although these guidelines have not been evaluated systematically in a prospective fashion, they represent an approach that is similar to current practice.

4. Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

Acute viral hepatitis. The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

Alcoholic and autoimmune hepatitis. Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).

Hepatobiliary disorders. Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

NASH. NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be

associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.

Cardiovascular causes. Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.

Concomitant treatments. It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

5. Follow-Up to Resolution

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

6. Re-challenge

Whether or not to re-challenge a subject who showed mild DILI is a difficult decision. Re-exposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with re-exposure. Re-challenge may not be considered negative unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A negative re-challenge does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of re-challenge to verify drug causation would give a false negative result.

Generally, re-challenge of subjects with significant AT elevations (>5xULN) should not be attempted. If such subjects are re-challenged, they should be followed closely. Re-challenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the re-challenge,

and the PI consulted.

APPENDIX E ACCEPTABLE BIRTH CONTROL METHODS

Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study. Moreover, women study participants are expected to use highly effective contraception for 6 months after the last dose of study drug and men are expected to use highly effective contraception for 6 months. Acceptable birth control methods are listed below.

Condom with spermicide and one of the following:

- Hormonal therapy (e.g. hormone implants) other than oral contraceptives
- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom+spermicide. Provided coils are copper-banded

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon, Norplan)+male condom with spermicide
- Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
- ntravaginal device+male condom with spermicide (eg, EE and etonogestrel)

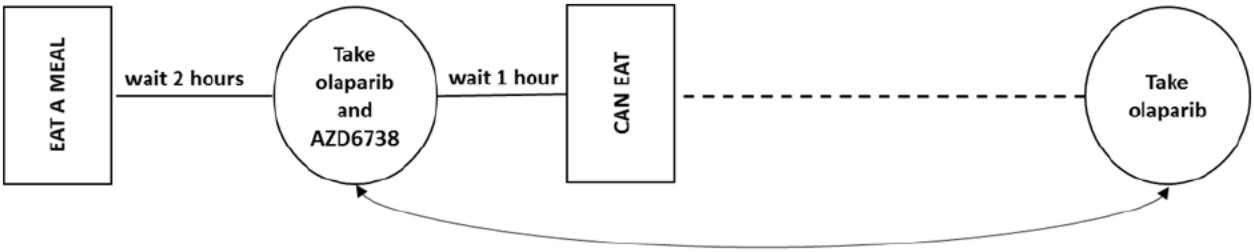
APPENDIX F STUDY DRUG DIARY

Treatment Diary for Olaparib and AZD6738

NCI 10222: A Phase II study of olaparib and AZD6738 in isocitrate dehydrogenase (IDH) mutant solid tumors

Study ID: _____ Cycle Number: _____
Olaparib Dose: _____mg BID AZD6738 Dose: _____mg

Instructions: Take your morning and evening dose of olaparib by mouth daily approximately 12 hours apart. Take your AZD6738 dose by mouth in the morning on days 1-7 of each 28 day cycle. Take the study drugs with one glass (8 oz) of water. Try to take your doses at roughly the same time each day. Do not eat for 2 hours before your AZD6738 dose or for at least 1 hour after.



If you miss a dose you can take it up to 2 hours before or after the scheduled dosing time. Do not double up on the missed dose. Do not take the missed dose if it is greater than 2 hours away from your scheduled dose time. If you vomit shortly after you swallow a tablet, you should only replace the dose if all the intact tablets can be seen and counted. Avoid grapefruit and St. John's Wort.

Day of cycle	Date	Time of Olaparib AM dose	Time of Olaparib PM dose	Time of AZD6738 (take in AM)	Notes
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					
Day 8				[redacted]	
Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
Day 15					
Day 16					
Day 17					
Day 18					
Day 19					
Day 20					
Day 21					

Day 22				[redacted]	
Day 23					
Day 24					
Day 25					
Day 26					
Day 27					
Day 28					

Diary reviewed by: (Print name) _____ Date _____

Signature: _____

APPENDIX G LABORATORY MANUAL

Testing / Storage Facilities

LC-MS detection and quantification of 2HG:	Jing Li, Ph.D. Pharmacology Core Karmanos Cancer Institute 4100 John R, HWCRC – room 523 Detroit, MI 48201 Phone: (313) 576-8258 Email: LiJing@wayne.edu
RNA and DNA sequencing:	Chris Karlovich Molecular Characterization (MoCha) Laboratory, Frederick National Laboratory for Cancer Research (FNLCR) Email: chris.karlovich@nih.gov
Multiplex immunofluorescence/ Imaging Mass Cytometry	Kurt A. Schalper, M.D. Ph.D. 310 Cedar St. BML113, Department of Pathology Yale School of Medicine New Haven, CT 06520-8023 Phone: 203-785-3588 Email: kurt.schalper@yale.edu

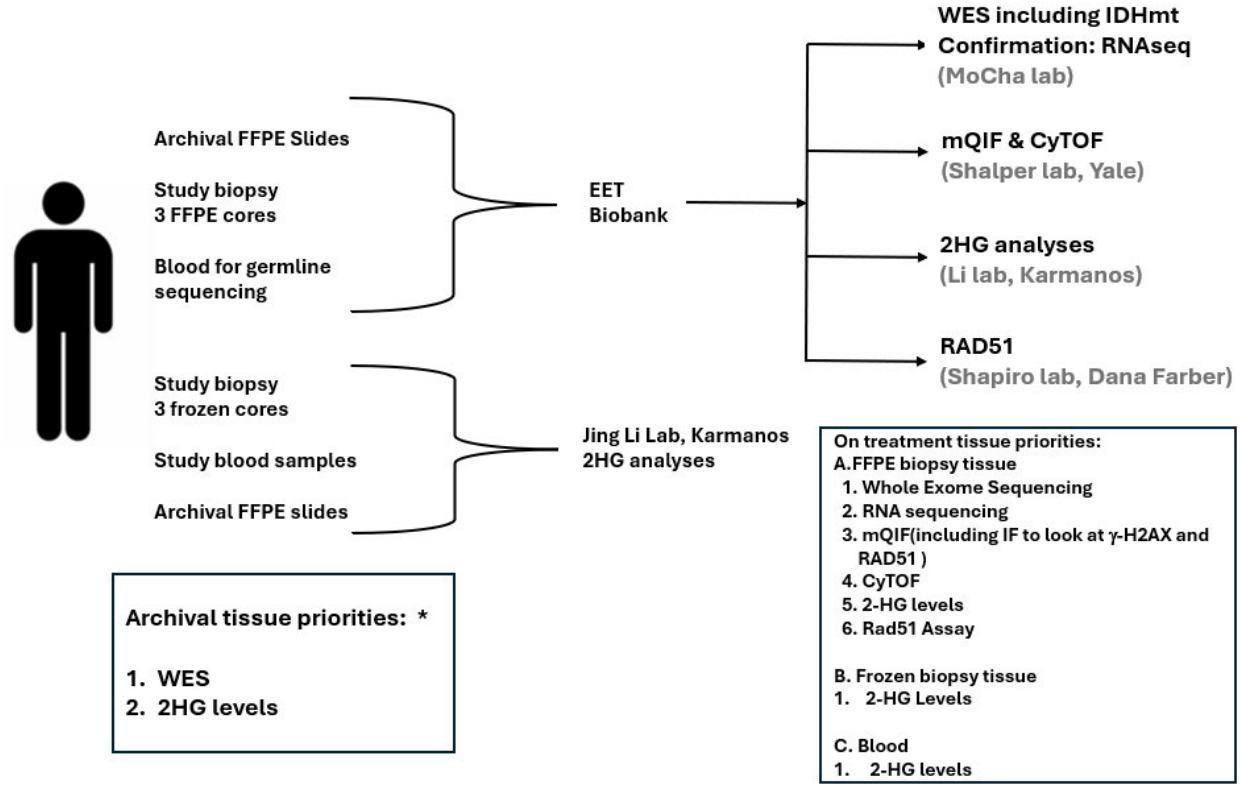
1. INTRODUCTION

This manual covers the procedures associated with acquisition of patient samples for correlative studies including processing, storage and shipment of these samples to central laboratories as required by the protocol.

Sample collection procedures for routine hematology, serum chemistry, coagulation parameters, pregnancy testing, and urinalysis samples etc. should be done as per local laboratories' requirements.

2. SAMPLE FLOW OVERVIEW

Tumor tissue (baseline biopsies/ on-treatment biopsies) and blood samples will be collected and sent to central laboratories for storage and analysis. The diagram below highlights the flow process for all lab samples.



*** Note: No archival or frozen tissue specimens were received directly by the Li Laboratory. Instead, (per Amendment 13 [version April 4, 2025]), the 2-HG assay will be performed using remaining FFPE tissue that was sent to the EET Biobank**

2.1 Summary Table for Specimen Collection

Time Point	Specimen and Quantity	Send Specimens to:
Pre-treatment (Day -14 to Day -1) After Registration		
	10 mL blood in EDTA tube 3 tissue cores in formalin-containing jars[1] If unable to collect a new biopsy, then submit formalin-fixed, paraffin-embedded (FFPE) archival tissue[2] from the primary tumor: 1 FFPE block (preferred), OR Slides from 1 FFPE block (serially sectioned and numbered: 1 H&E stained slide, 40 unstained, uncharged, unbaked 10-micron slides, 2 5-micron charged slides)	EET Biobank
	3 flash frozen tissue cores[1] 4 mL blood in purple top EDTA tubes[3], processed for plasma (4 aliquots) & buffy coat, and frozen FFPE archival tissue from the primary tumor: 5 unstained 10-micron slides, if available[2]	Pharmacology Core at Karmanos Cancer Institute
After Cycle 1 Week 4 (+ / - 7 days)		
	3 tissue cores in formalin-containing jars[1]	EET Biobank
	3 flash frozen tissue cores[1]	Pharmacology Core at Karmanos Cancer Institute
Cycle 2 Day 1 (prior to olaparib dosing)		
	4 mL blood[3] in purple top EDTA tubes, processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core at Karmanos Cancer Institute
Cycle 4 Day 1 (prior to olaparib dosing)		
	4 mL blood[3] in purple top EDTA tubes, processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core at Karmanos Cancer Institute
Cycle 8 Day 1 (prior to olaparib dosing)		
	4 mL blood[3] in purple top EDTA tubes, processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core at Karmanos Cancer Institute
End of Study/Progression/Relapse		
	4 mL blood in purple top EDTA tubes[3], processed for plasma (4 aliquots) & buffy coat, and frozen	Pharmacology Core Karmanos Cancer Institute

[1]For new biopsies, the Tissue Biopsy Verification Form (Appendix G, Section 8), a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank.
[2] For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. If a patient does not consent to biopsies and only a block is available the site should cut 5 slides for 2HG and send these to Dr. Li, and send the remainder of the block to the biorepository for use by MoCha, Frederick National Laboratory for Cancer

Research (FNLCR). If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 46).
[3] Draw blood prior to olaparib dosing.

Prioritization for use of tumor tissue and blood specimens will be as follows:

1. DNA whole exome sequencing
2. RNA sequencing
3. mQIF/CyTOF-IMC studies (including IF to look at γ-H2AX and RAD51)
4. 2-HG measurement
5. RAD51 assay

Any specimens remaining after the above-prioritized studies will be sent to Yale for consideration of additional prioritization or sample use strategies based on individual sample characteristics and quality after central pathology review at Yale. Any remaining specimens will be banked at Yale University.

3. PLANNED SAMPLE ANALYSIS

Serial blood samples and tissue from tumor biopsies will be collected and analyzed to include the following work:

Testing Facility	**Platform**	**Biomarker/Correlative**
Li Lab, Karmanos	LC-MS/MS	Determination of 2-HG in tissue and plasma
MoCha, Frederick National Laboratory for Cancer Research (FNLCR)	Illumina-based next-generation sequencing	DNA whole exome sequencing and RNA transcriptomic sequencing
Schalper Lab, Yale	mQIF and CyTOF-IMC	In situ analysis of tumor DNA repair markers
Shapiro Lab, Dana-Farber	Immunohistochemistry	Detection of Geminin and RAD51

4. SAMPLING TIME POINTS

4.1 Tumor Tissue Sample Collection Time Points

Time Point	Note
Pre-treatment (Day -14 to Day -1)	Biopsy performed after patient is registered on study.

After 1 cycle of treatment (4 weeks, +/- 7 days)	On treatment biopsy

4.2 Blood Sample Time Points

4.2.1 Blood for 2-HG Collection Time Points

All patients will have blood collected for LC-MS detection and quantification of 2HG in plasma.

Time Point	Note
Pre-treatment (Day -14 to Day -1)	Blood drawn after study registration.
Cycle 2 Day 1	Blood drawn prior to olaparib dosing.
Cycle 4 Day 1	
Cycle 8 Day 1	
Time of tumor progression/relapse or End of study	Blood drawn at End of Treatment visit

4.2.2 Blood for Germline Mutation Analysis

Time Point	Note
Screening (Day -14 to Day -1)	Blood drawn after study registration.

5. SAMPLE COLLECTION, PROCESSING AND SHIPPING PROCEDURES

5.1 Specimen Procurement Kits and Scheduling

5.1.1 Specimen Shipping Kits

Kits for the collection and shipment of specimens to the EET Biobank can be ordered online via the Kit Management system: (https://kits.bpc-apps.nchri.org/).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the EET Biobank. Institutional supplies must be used for all other specimen collection and processing.

5.1.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:
Tumor tissue specimens fixed in formalin must be shipped on the same day of collection. Tissue can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.
Tumor and blood specimens submitted frozen can be collected on any day but must be stored frozen and shipped to the Jing Li laboratory at the Karmanos Cancer Institute on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained at -80°C.
Fresh blood specimens may be collected and shipped to the EET Biobank Monday through Friday.

5.2 Specimen Tracking System Instructions

5.2.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies without a corresponding pathology report, the radiology and operative report(s) must also be uploaded into Rave, when available. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

5.2.2 Specimen Labeling

5.2.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date and time (to be added by hand)
- CTEP Protocol Number (NCI#10222) – Blood Samples for 2-HG ONLY

5.2.2.2 Tissue Specimen Labels

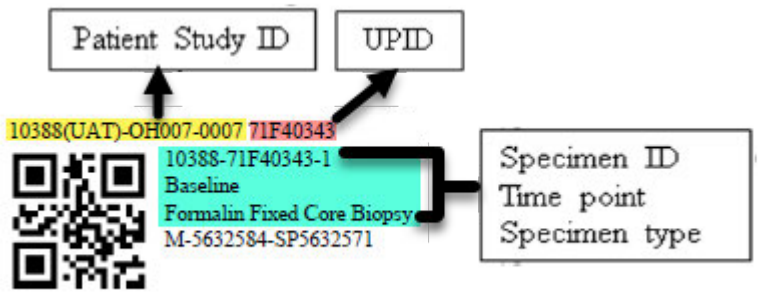
Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, tissue in formalin-containing jars)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (when applicable)
- Collection date and time (to be added by hand)
- Slide section number (only if archival tissue is submitted as slides)(to be added by hand)

5.2.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5” high and 1.28” wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.2.3 Overview of Process at Treating Site

5.2.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.2.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date and time on each label. After collection, store labeled specimens as described in Appendix G, Section 5.2.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), and Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or the Tissue Biopsy Verification form (Appendix G, section 8). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number, diagnosis or relevant dates (such as collection date) and include the UPID and patient study ID on each document (either by adding a label or hand writing).

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.3 Tumor Tissue Sample Collection

The tumor tissue will be obtained by a surgical biopsy or imaging-guided biopsy. In the instance that a patient has multiple measurable lesions, tumor biopsies will be performed on the most accessible site of disease. Each biopsy will consist of 6 passes of a large gauge needle (such as 16 or 18 gauge); each core should be at least 1 cm in length.

For each set of biopsies, 3 of the tumor cores will be formalin-fixed on site and sent to the EET Biobank, where they will be processed. 3 of the tumor cores will be flash frozen on site and sent directly to the Jing Li laboratory at the Karmanos Cancer Institute. If fewer than 6 cores are obtained, the cores will be divided evenly among formalin-fixed and flash frozen.

5.3.1 Processing of formalin-fixed tissue samples

Three (3) tissue cores are shipped in formalin on the same day as collection to the EET Biobank (see section 5.6). Specimens should be placed immediately into buffered formalin (provided in the kit) in the provided specimen collection container and handled as follows:

Label formalin-filled containers according to instructions in section 5.2.1.
Place one core in each cassette.
Snap the cassette lids closed and place cassettes into a formalin-filled pre-labeled container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.
Secure the container lids and place the containers into the shipping kit. Keep tissue in formalin jars at room temperature until shipment to the EET Biobank.

5.3.2 Processing of frozen tissue samples

Immediately after tissue collection, transfer 3 cores of biopsy tissue to a **screw-cap polypropylene cryogenic tube with external threads** and snap-freeze in liquid nitrogen.
Label the tubes according to instructions in section 5.2.1.
These tumor specimens (3 cores) should be stored at -80°C until shipment directly to the

Karmanos Cancer Institute Pharmacology Core.

5.4 Blood Sample Collection for Germline Mutation Analysis

5.4.1 Collection of Blood in EDTA Tubes

Label EDTA tubes according to the instructions in section 5.2.1.
Collect 10 mL blood in EDTA tube and gently invert tube to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. (See Summary Table for Specimen Collection in Section 2 for amounts at each time point).
Ship on day of collection (whenever possible) according to instructions below.
If blood cannot be shipped on the day of collection (*e.g.*, a late scheduled collection), then refrigerate until shipment.

5.5 Blood Sample Collection for Determination of 2-HG

Blood samples (4 mL at each time point) will be collected into EDTA tubes. Blood in EDTA tubes will be immediately placed on ice or refrigerated at 4°C until processed. The actual day and time of sample collection will be recorded on the "Shipping Manifest/Case Report Form for 2-HG Blood Samples" (FORM A), which contains information on patient study number, diagnosis, age, weight, treatment (dose and time), blood sample collection day and time.

Within 1 hour of collection, the blood sample will be centrifuged at 4°C, at 3000 rpm for 10 minutes. Immediately after centrifugation, plasma will be transferred to four screw-cap polypropylene cryogenic tubes with external threads (four aliquots, ~0.5 ml per aliquot), and blood cells will be kept in the original tube. The tubes will be labeled with the patient's initials, study number, sample collection day and time. All samples will be stored at -80°C until shipment. Blood samples will be processed at the study sites. ***Note: Both plasma and blood cell samples will be shipped*** directly to Karmanos Cancer Institute Pharmacology Core.

5.6 Shipping Specimens from Clinical Site to the EET Biobank

Core biopsies that are fixed in formalin and fresh whole blood should be shipped as one shipment at ambient temperature, whenever possible. The same box sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For formalin-fixed biopsies, if the corresponding anatomical pathology report is not available at the time of shipment, then the operative and/or radiology report must be uploaded to the ETCTN specimen tracking system and included in the package, or the specimen will not be processed.

5.6.1 Required Forms for Specimen Submissions

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	**Required Forms**
Archival	3. Shipping List 4. Corresponding Pathology Report

Tissue	Required Forms
New Biopsy	5. Shipping List 6. Tissue Biopsy Verification Form (Appendix G, Section 8) 7. Diagnostic Pathology Report 8. Operative and/or Radiology Report
Blood	1. Shipping List

5.6.2 Specimen Shipping Instructions

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.
Archival FFPE tissue may be shipped Monday through Thursday.
Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

5.6.2.1 Shipping Ambient Tissue and Blood in a Single Chamber Kit

Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed. Formalin jars should be wrapped in parafilm.
Place the specimens in zip-lock bags. Use a separate bag for each specimen type.
Place specimens into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
Place the specimen(s) and a copy of the shipping manifest and corresponding reports such as operative or radiology reports into the insulated shipping container. In winter months please include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
Place the lid on top of the container. Close the outer flaps and tape shut.
Attach a shipping label to the top of the shipping container.
Attach an Exempt Human Specimen sticker to the side of the container.
Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.3 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
2200 International Street
Columbus, OH 43228
PH: (614) 722-2865
FAX: (614) 722-2897

Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

5.4 Shipping Specimens from Clinical Site to the Li Lab (Blood and 3 frozen cores for 2-HG)

3 frozen cores and plasma and blood cell samples collected for determination of 2-HG will be shipped directly to Karmanos Cancer Institute Pharmacology Core at the following address:

Attn: Jing Li
Pharmacology Core
Karmanos Cancer Institute
4100 John R, HWCRC – room 523
Detroit, MI 48201
Phone: (313) 576-8258
Email: LiJing@wayne.edu

For shipping, all frozen plasma and blood samples should be placed in cardboard tray/box so samples remain upright. This tray/box is to be placed in a Styrofoam carton with 10-15 lbs of dry ice (block with or without pellets) to keep samples frozen during shipping. A copy of the "Shipping Manifest/Case Report Form for 2-HG Blood Samples" (Form A), should be in the shipping box, reflecting the samples that are being sent. Samples should be shipped via **FedEx Priority Overnight** service. Please notify Jing Li via email (LiJing@wayne.edu) when samples are shipped and include the shipment tracking number.

Samples can be batched and shipped.

6 CONTACT INFORMATION

Please contact the team members listed below for any questions on sample collection, processing, storage and shipment.

Study Coordinator	Yale University / Yale Cancer Center	Ingrid Palma Phone: (203) 737-5342 Fax: (203) 785-4069 Email: ingrid.palma@yale.edu
Study PI	Yale University	Patricia M. LoRusso, D.O., Associate Director for Experimental Therapeutics Yale Cancer Center 333 Cedar St PO Box 208028 New Haven, CT 06520-8028 Office Number: 203-785-5944 Fax: 203-785-4116
Tumor Tissue	Yale University	Kurt A. Schalper, M.D., Ph.D. 310 Cedar St. BML113 Department of Pathology Yale School of Medicine New Haven, CT 06520-8023 Phone: 203-785-3588 Email: kurt.schalper@yale.edu
Plasma for 2-HG	Karmanos Cancer Institute	Jing Li, Ph.D. Pharmacology Core Karmanos Cancer Institute 4100 John R, HWCRC – room 523 Detroit, MI 48201 Phone: (313) 576-8258 Email: LiJing@wayne.edu
Tumor Tissue, Liquid Biopsy (ctDNA) & Blood for Germline Mutation Shipping	EET Biobank	EET Biobank Phone: (614) 722-2865 Email: BPCBank@nationwidechildrens.org
DNA and RNA sequencing	MoCha Laboratory, Frederick National Laboratory for Cancer Research (FNLCR)	Chris Karlovich Email: chris.karlovich@nih.gov

7 SHIPPING FORM (FROZEN TISSUE SPECIMENS AND BLOOD FOR 2-HG SAMPLES)

Please copy this form for multiple shipments.

Pre-printed label for research samples should contain:

CTEP Protocol Number (NCI#10222)
Collection Time Point
Patient Study ID Number
Date of Collection
Time of Collection

Ship From: Laboratory PI Address Contact Name Contact Phone Contact Email	NCI#10222 Karmanos Cancer Institute Shipping Manifest	Ship To: Attn: Jing Li Pharmacology Core Karmanos Cancer Institute 4100 John R, HWCRC – room 523 Detroit, MI 48201 Phone: (313) 576-8258 Email: LiJing@wayne.edu

Shipping Date: Clinical Protocol: Carrier: Shipping #:

In Package	#	Patient Study ID #	Diagnosis	Age	Weight	Treatment (Dose & Time)	Collection Time Point	Collection Time	Collection Date MM/DD/YYYY
☐	Test	2007-014-21	Cholangiocarcinoma	69	60 kg	300 mg, 05/26/2018 @ 20:00	C2D1	09:15	05/27/2018
☐	1								
☐	2								
☐	3								
☐	4								
☐	5								
☐	6								
☐	7								
☐	8								
☐	9								
☐	10								

Notify the following people prior to shipping samples: Jing Li: LiJing@wayne.edu **Include the shipment tracking number in email**

8 TISSUE BIOPSY VERIFICATION

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the EET Biobank.

If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.

Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Primary Metastatic

Time point (circle one): Pre-treatment After Cycle 1

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

_____ _____
Clinician Signature Date

_____
Clinician Printed Name

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.

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