Title: OLAParib COmbinations

ClinicalTrials.gov ID: NCT02576444

Protocol Date: 2/7/2019

Abstract

[The abstract should be one paragraph of between 150 and 250 words. It is not indented. Section titles, such as the word *Abstract* above, are not considered headings so they don't use bold heading format. Instead, use the Section Title style. This style automatically starts your section on a new page, so you don't have to add page breaks. Note that all of the styles for this template are available on the Home tab of the ribbon, in the Styles gallery.]

Keywords: [Click here to add keywords.]

Title: OLAParib COmbinations

[The body of your paper uses a half-inch first line indent and is double-spaced. APA style provides for up to five heading levels, shown in the paragraphs that follow. Note that the word *Introduction* should not be used as an initial heading, as it's assumed that your paper begins with an introduction.]

[Heading 1]

[The first two heading levels get their own paragraph, as shown here. Headings 3, 4, and 5 are run-in headings used at the beginning of the paragraph.]

[Heading 2][1]

[To add a table of contents (TOC), apply the appropriate heading style to just the heading text at the start of a paragraph and it will show up in your TOC. To do this, select the text for your heading. Then, on the Home tab, in the Styles gallery, click the style you need.]

[Heading 3].

[Include a period at the end of a run-in heading. Note that you can include consecutive paragraphs with their own headings, where appropriate.]

[Heading 4].

[When using headings, don't skip levels. If you need a heading 3, 4, or 5 with no text following it before the next heading, just add a period at the end of the heading and then start a new paragraph for the subheading and its text.] (Last Name, Year)

[Heading 5].

[Like all sections of your paper, references start on their own page. The references page that follows is created using the Citations & Bibliography feature, available on the References tab. This feature includes a style option that formats your references for APA 6th Edition. You

can also use this feature to add in-text citations that are linked to your source, such as those shown at the end of this paragraph and the preceding paragraph. To customize a citation, right-click it and then click Edit Citation.] (Last Name, Year)

References

Last Name, F. M. (Year). Article Title. *Journal Title*, Pages From - To.

Last Name, F. M. (Year). *Book Title.* City Name: Publisher Name.

Footnotes

[1][Add footnotes, if any, on their own page following references. For APA formatting requirements, it's easy to just type your own footnote references and notes. To format a footnote reference, select the number and then, on the Home tab, in the Styles gallery, click Footnote Reference. The body of a footnote, such as this example, uses the Normal text style. *(Note: If you delete this sample footnote, don't forget to delete its in-text reference as well. That's at the end of the sample Heading 2 paragraph on the first page of body content in this template.)*]

Tables

Table 1

[Table Title]

Column Head	Column Head	Column Head	Column Head	Column Head
Row Head	123	123	123	123
Row Head	456	456	456	456
Row Head	789	789	789	789
Row Head	123	123	123	123
Row Head	456	456	456	456
Row Head	789	789	789	789

Note: [Place all tables for your paper in a tables section, following references (and, if applicable, footnotes). Start a new page for each table, include a table number and table title for each, as shown on this page. All explanatory text appears in a table note that follows the table, such as this one. Use the Table/Figure style, available on the Home tab, in the Styles gallery, to get the spacing between table and note. Tables in APA format can use single or 1.5 line spacing. Include a heading for every row and column, even if the content seems obvious. A default table style has been setup for this template that fits APA guidelines. To insert a table, on the Insert tab, click Table.]

Figures title:

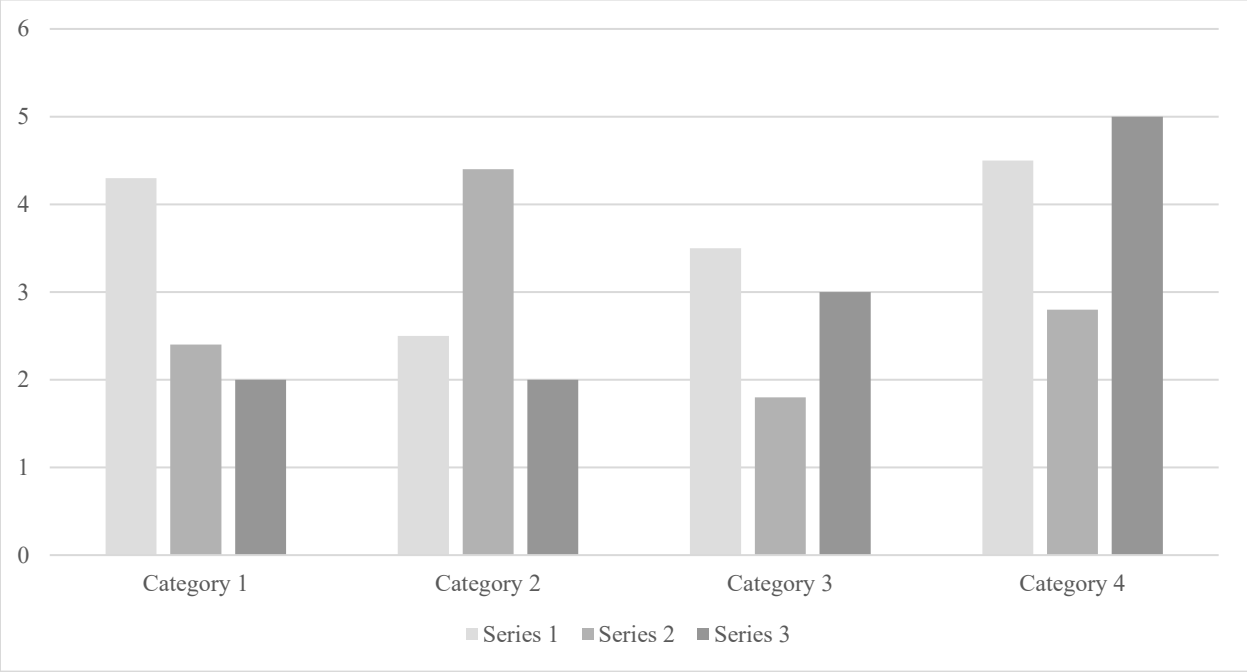


Figure 1. [Include all figures in their own section, following references (and footnotes and tables, if applicable). Include a numbered caption for each figure. Use the Table/Figure style for easy spacing between figure and caption.]

For more information about all elements of APA formatting, please consult the *APA Style Manual, 6th Edition*.

Yale CANCER CENTER

A Comprehensive Cancer Center Designated by the National Cancer Institute

Drug Substances	Olaparib (AZD2281), AZD5363, AZD6738, AZD1775
Version Number	6.0
Date	07 February 2019
Local Protocol #	HIC#1508016363
IND#	128100

A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination with AZD1775, AZD5363, or AZD6738 in Advanced Solid Tumors - OLAPCO (OLAParib COmbinations)

PROTOCOL SYNOPSIS

TITLE: A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination with AZD1775, AZD5363, or AZD6738 in Advanced Solid Tumors- OLAPCO (OLAParib COmbinations)

Principal Investigator:
Joseph Paul Eder, M.D.
Professor of Medicine
Director, Early Drug Development Program
Yale University Cancer Center
333 Cedar Street
WWW211, PO Box 208028
New Haven, CT 06520
Direct: (203) 737-1906
Cell: (203) 500-1019
Email: joseph.eder@yale.edu

Coordinating Center: Yale Cancer Center

Participating Institutions: Dana-Farber/Harvard Cancer Center (DF/HCC)
Boston, MA
Vanderbilt Ingram Cancer Center, Nashville, TN
Cleveland Clinic, Cleveland, OH

Objectives

Primary Objective

- To determine tumor overall response rate (ORR) in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment across tumor types in each arm of the study (Note: there will be no formal comparison between arms)

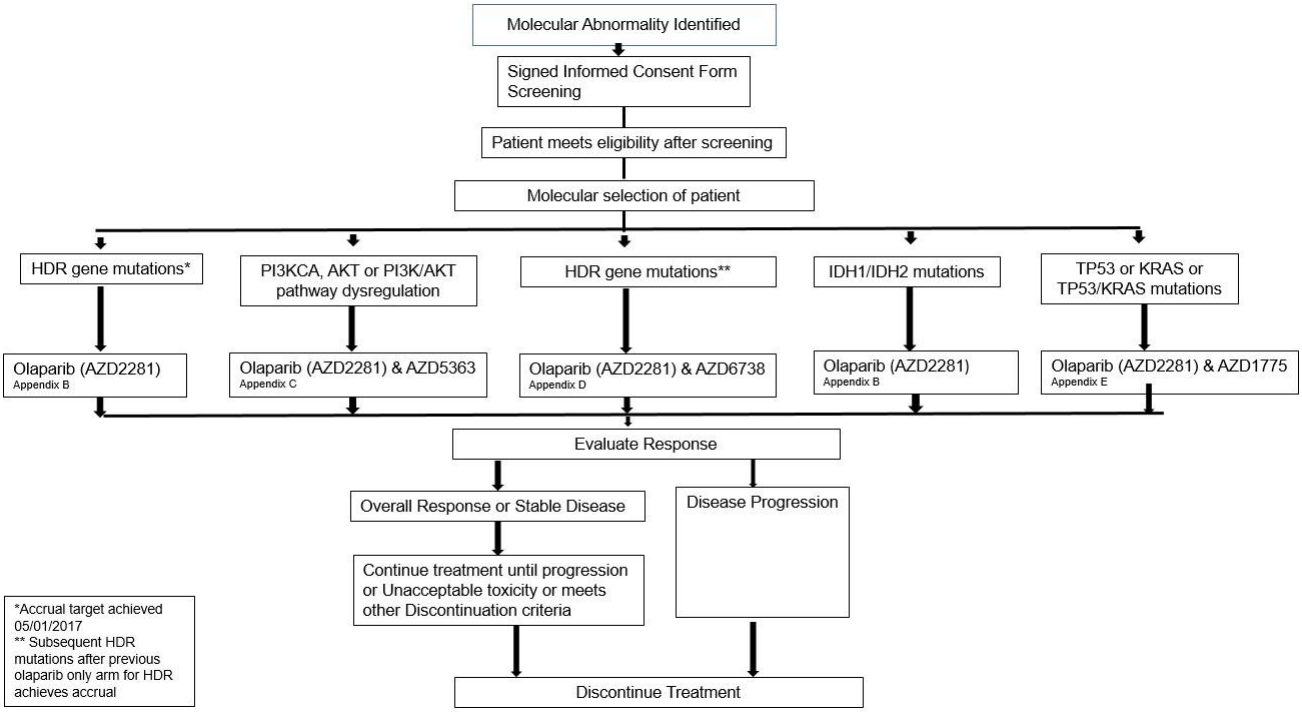
Secondary Objectives

- To determine tumor overall response rate (ORR) in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment within tumor type in each arm of the study (Note: there will be no formal comparison between arms)
- To determine tumor clinical benefit rate (CBR) in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment across tumor types and within tumor type in each arm of the study (Note: there will be no formal comparison between arms)
- To determine progression free survival (PFS), duration of overall response, and duration of stable disease in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment across tumor types and within tumor type in each arm of the study (Note: there will be no formal comparison between arms)
- To determine the safety and tolerability of oral administration of olaparib alone and in combination of AZD1775, AZD5363, and AZD6738 in patients with advanced solid tumors
- To collect and store molecular profiling data of all patients enrolled in this study, for the purpose of correlating treatment response/clinical benefit with patterns of tumor genetic abnormalities in tumors

Exploratory Objectives

- To correlate clinical benefit rate (CBR) associated with treatment at Week 16 (Overall Response Rate (ORR), Complete Response (CR), and Partial Response (PR)) with additional defects in DNA repair pathways as measured by genetic aberrations in the tumors
- To compare genetic variants/mutations measured in tumor tissue in diagnostic archival specimen at baseline and on progression (when samples available), and correlate with tumor response and clinical benefit
- To determine tumor mutations in ctDNA at baseline, on treatment, and at progression, and evaluate the changes in ctDNA mutations and correlate with tumor response and clinical benefit

Study Design



This is a phase II signal-searching study in a range of tumor types with the potential to identify novel tumor indications for combination therapy with olaparib that can subsequently be explored in dedicated studies. Patients will be enrolled in this study based on molecular markers from genetic profiling performed prior to study entry (outside of protocol). The trial will also identify genetic determinants of response and resistance.

Patients with tumors harboring damaging mutations in Homologous – DNA repair (HDR) genes or mutations *such as ATM, CHK2, MRN (MRE11/NBS1/RAD50), CDKN2A/B, and APOBEC* will be treated with olaparib or olaparib and AZD6738. Enrollment to the olaparib monotherapy arm will be completed prior to commencement of enrollment to the olaparib and AZD6738 arm. Patients with tumors harboring IDH1/IDH2 mutations will be treated with olaparib. Patients with tumors harboring either *TP53* or *KRAS* mutations or mutations in *KRAS* and *TP53* will be treated with AZD1775 plus olaparib. Patients with tumors harboring *PTEN*, *PIK3CA*, *AKT,* or *ARID1A* mutations or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway will be treated with AZD5363 plus olaparib.

The recommended phase II doses of olaparib and the ATR inhibitor AZD6738 has recently been established. This combination will replace the combination of olaparib and AZD 2014 for programmatic reasons (a more homologous DNA repair/HDR focused agent in AZD6738 and re-ordered priorities within AstraZeneca).

The doses for AZD1775 plus olaparib is not yet available. A Phase I clinical trial is currently under way to determine the recommended phase II doses for this combination. The AZD1775 plus olaparib will be added as a further addendum to the protocol and opened once the recommended phase II doses are available.

A minimum of 80 subjects and a maximum of 125 subjects will be enrolled in this study, with each arm enrolling a minimum of 16 subjects and a maximum of 25 subjects depending on ORR in the first 16 patients treated in each arm. Treatment assignment to each arm is non-randomized, and

dependent on the presence of molecular markers from genetic profiling. If a patient's tumor is found to have multiple mutations (*TP53* and *PIK3CA*, for example) meeting criteria for multiple arms, the decision of which arm to enroll the patient should be made by the treating physician. These decisions should also be made in conjunction with the PI. Treatment groups include olaparib, AZD1775 plus olaparib, AZD5363 plus olaparib, and AZD6738 plus olaparib.

This protocol consists of the main protocol applicable across all arms, as well as appendices that are specific to the 4 treatment arms:

- Olaparib (B)
- AZD5363 plus olaparib (C)
- AZD6738 plus olaparib (D)
- The AZD1775 plus olaparib and arm will be added as a further addendum to the protocol and opened once the recommended phase II doses are available.

Investigational product, dosage and mode of administration

Olaparib

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib to the investigator as round or oval green film-coated tablets.

Patients will be administered olaparib orally twice daily (bid) at 300 mg. Two (2) x 150 mg olaparib tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Combination drug should be given at least 1 hour after the patient has taken their olaparib. Dose reductions will be managed with 100 mg and 150 mg tablets.

AZD5363

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply AZD5363 to the investigator as beige film-coated tablets.

Patients will be administered AZD5363 at 640 mg twice daily for two days on/five days off (2/7) schedule. Two (2) 200 mg tablets and three (3) 80 mg tablets should be taken twice daily. The AZD5363 tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Patients should fast for 2 hours before doing and for 1 hour after dosing. AZD5363 should be given at least 1 hour after the patient has taken their olaparib dose. Dose reductions will be managed with 80 mg tablets.

AZD6738

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply AZD6738 to the investigator as round white tablets.

Patients will be administered AZD6738 at 160 mg daily for days 1-7 of a 28-day cycle (7/28) schedule. AZD6738 is available as 100, 20 and 10 mg tablets. Tablets should be taken daily. 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. When olaparib is given on its own, the olaparib table3t formulation can be given without regard to food. Dose reductions will be managed with

existing tablets.

Duration of Treatment

Treatment may continue indefinitely or until one of the following criteria applies:

- Objective disease progression according to RECIST v1.1 criteria
- Unacceptable adverse event(s)
- Significant treatment delays > 4 weeks due to adverse events determined to be probably/definitely attributed to a study agent
- Intercurrent illness that prevents further administration of treatment
- Severe non-compliance to study protocol as judged by the investigator
- Patient becomes pregnant
- Patient is determined to no longer meet the required inclusion/exclusion criteria for the study
- Patient decided to withdraw from the study (the subject is at any time free to discontinue

  treatment, without further prejudice to further treatment)
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Duration of Follow Up

Patients will be followed for 30 days after removal from study or until death, whichever occurs first. Patients will be followed every 12 weeks (+/- 1 week) thereafter by phone for survival status. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Outcome Variable(s)

Primary outcome variable: ORR by RECIST v1.1 at 16 weeks from starting study treatment

Safety outcome variables: Adverse Events (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and hematology.

Secondary outcome variables:

- CBR
- PFS
- Duration of overall response
- Duration of stable disease
- Collecting/storing molecular profiling data on all patients

Exploratory outcome variables:

- Correlating CBR with ORR, CR, and PR with additional defects in DNA repair pathways in tumors
- Comparing genetic variations/mutations at baseline and at progression and correlating with response/clinical outcome
- Measuring ctDNA mutations at baseline, on treatment, and at progression and correlating changes in ctDNA mutations with response/clinical benefit
- Potential retrospective biomarker research

Statistical Methods

Sample Size Justification and Decision Rules

The sample size estimation for each single arm of this phase II study is based on the objective response rate (ORR). A two-stage "minimax" accrual design described by Simon will minimize the maximum number of patients exposed to treatment for a set of assumed values of the design parameters [41]. These parameters are: (i) probability of response ≤ p_0, where p_0 defines the ineffective treatment response proportion, (ii) probability of response ≥ p_1, where p_1 defines the effective treatment response proportion, (iii) *power* = 1 - probability of Type II error, and (iv) α = probability of Type I error. For this study, the assumed design parameters are p_0 = 0.10, p_1 = 0.30, *power* = 0.90, α = 0.10. If there is evidence at the conclusion of stage 1 or stage 2, that the true underlying ORR is at least 30% for a treatment arm, consideration will be given for further testing of that treatment. However, if the results at the conclusion of stage 1 provide evidence that the treatment is inactive in patients, i.e. ORR less than 10%, then the treatment arm will be terminated early.

From the design parameters given above we derive the two-stage sample sizes and decision rules. Stage 1: Initially, 16 patients per arm will be enrolled into the study and treated at stage 1. If there are less than 2 responses among these first 16 subjects, accrual to the treatment arm will be terminated based on evidence that it is likely that ORR ≤ 10% and unlikely that ORR ≥ 30%. If there are at least 5 responses among the first 16 patients, recruitment to 25 patients will continue in the treatment arm, but further development may be considered. If there are at least two but less than 5 responses in these first 16 patients, the trial will continue to stage 2 for the treatment arm until 25 patients have been treated. If there are at least 5 responses in these 25 patients, then further development of the treatment will be considered.

Some additional operating characteristics for this design are: expected number (i.e. frequentist mean number) of patients exposed when true ORR is 10% = 20.4; expected number of patients exposed when true ORR is 30% = 24.8; the probability of early termination for futility when true ORR is 10% = 0.515; the probability of early termination for futility when true ORR is 30% = 0.026.

This design provides 90% statistical power to detect a difference of 20% (successful treatment = 30% vs. futile treatment = 10%) with a type I error probability less than 0.10.

Early Stopping Rule for Safety

We will monitor the study for safety in the first 16 patients in each single arm. If we observe 4 or more patients with unacceptable toxicity in the first 16 patients, then the arm will be terminated early. Unacceptable toxicity is defined for this protocol as CTCAE Grade 4 hematological and CTCAE Grade 3 non- hematological toxicities that fail to resolve to Grade 1 despite appropriate supportive care. With this design, the probability of terminating any arm early is 0.07 if the true but unknown unacceptable toxicity rate is 10%, and 0.75 if the true toxicity rate is 30%.

Analysis Sets

Full Analysis Set: all enrolled patients.
Safety Analysis Set: all patients who receive at least one treatment dose.
Efficacy Analysis Set: all patients who receive at least one treatment dose and are evaluable for post- baseline response status.

General Methods

Analyses will be performed separately for each treatment arm, as if they are four parallel studies within one protocol.

Descriptive statistics, including means, standard deviations, medians and ranges for continuous scale parameters, as well as percent and frequencies for categorical parameters, will be presented. For time-to-event parameters, estimates of median survival with 95% confidence intervals will be calculated, and Kaplan Meier plots will be provided. 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.

No corrections for multiplicity will be performed.

Disposition, Demographics, and Baseline Clinical Characteristics (Full Analysis Set)

Patient disposition will be listed and tabulated by treatment arm. Demographic information including but not limited to age, gender and race, will be tabulated by treatment arm. Other baseline characteristics, such as medical history, concomitant medications, disease severity, time from diagnosis, physical exam and lab test results will be presented similarly.

Safety and Toxicity (Safety Analysis Set)

Adverse events (AEs) will be listed and tabulated by treatment arm. AEs will be classified based on the likelihood that they are treatment-related. NCI toxicity Grade 3 and Grade 4 laboratory abnormalities will also be listed. PFS analysis will also be performed with patients in the safety analysis set.

Efficacy (Efficacy Analysis Set)

The efficacy of each treatment will be assessed by analysis of the primary endpoint using the 16-week response status. The exact Binomial method will be used to calculate two-sided 95% confidence intervals for ORR. Multivariate logistic regression will be used to predict the ORR by including patient characteristics variables and other clinically relevant factors as covariates.

For time-to-event endpoints, Kaplan-Meier plots and estimates for median survival time with 95% confidence intervals will be provided for each treatment arm.

Subgroup Analyses

Due to the limitation of the sample size, we will not have sufficient power to perform official statistical tests to detect differences between patients with different tumor types or mutations. Descriptive statistics will be used to present ORR by tumor type and by specific mutation. Data permitting, survival function of patients in subgroups will also be summarized.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Full text
ADP	Adenosine diphosphate ribose
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
AZ	AstraZeneca
BER	base excision repair
bid	twice daily dosing
bp	base pair
C	Celsius
ctDNA	circulating tumor DNA
CBC	complete blood count
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CLIA	Clinical Laboratory Improvement Amendment
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
d	Day
DDR	DNA damage repair
DF/HCC	Dana-Farber/Harvard Cancer Center
dL	deciliter
DNA	deoxyribonucleic acid
DSB	double strand breaks
DSMC	Data and Safety Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram
eCRF	electronic case report form
EKG	electrocardiogram
FDA	Food and Drug Administration
FH	Fumarate Hydratase
GBM	Glioblastoma multiforme
HCT	hematocrit
HER2	human epidermal growth factor receptor 2
Hgb	hemoglobin
HbgA1c	glycated hemoglobin
HIC	Human Investigation Committee
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HDR	Homologous DNA recombination
HDRD	Homologous DNA recombination deficient
HDRR	Homologous DNA recombination repair
ICL	interstrand crosslinks
IHC	immunohistochemistry
IND	Investigational New Drug

INR	International Normalized Ratio
IRB	Institutional Review Board
ISS	Investigator Sponsored Study
kg	kilogram
L	liter
LVEF	left ventricular ejection fraction
m	meters
mcg	microgram
MDS	Myelodysplastic syndrome
mg	milligram
MI	myocardial infarction
miRNA	micro ribonucleic acid
mL	milliliter
mmol	millimoles
MMR	mismatch repair
MMTV	mouse mammary tumor virus
ms, msec	milliseconds
MTD	maximum tolerated dose
mTOR	mammalian Target of Rapamycin
MUGA	multi-gated acquisition scan
NAD	Nicotinamide adenine dinucleotide
NCI	National Cancer Institute
NER	nucleotide excision repair
NGS	next-generation sequencing
NHEJ	non-homologous end joining
NYHA	New York Heart Association
OAE	other significant adverse event
OLAPCO	Olaparib Combinations
ORR	overall response rate
PARP	poly(ADP-ribose) polymerase
PD	progressive disease
Ph	phase
PI	principal investigator
PI3K	phosphotidylinositol 3-kinase
PK	protein kinase
PO	Orally
PR	partial response
PRMC	Protocol Review and Monitoring Committee
PS	performance status
PTEN	Phosphatase and tensin homolog
PLT	Platelet
PTT	partial thromboplastin time
QD	Once per day
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase II dose
RT-PCR	real-time polymerase chain reaction
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase

SGPT	serum glutamate pyruvate transaminase
SOP	standard operating procedures
SSB	single-strand breaks
$t_{1/2}$	terminal half-life
TBID	to be determined
TNBC	triple negative breast cancer
ul	microliter
ULN	upper limit of normal
US	Ultrasound
UV	ultraviolet
WBC	white blood cells
YCC	Yale Cancer Center

1 OBJECTIVES

1.1 Primary Objectives

- To determine tumor overall response rate (ORR) in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment across tumor types in each arm of the study (Note: there will be no formal comparison between arms)

1.2 Secondary Objectives

- To determine tumor overall response rate (ORR) in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment within tumor type in each arm of the study (Note: there will be no formal comparison between arms)
- To determine tumor clinical benefit rate (CBR) rate in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment across tumor types and within tumor type in each arm of the study (Note: there will be no formal comparison between arms)
- To determine progression free survival (PFS), duration of overall response, and duration of stable disease in molecularly selected patients with measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST), before versus after 16 weeks of treatment across tumor types and within tumor type in each arm of the study (Note: there will be no formal comparison between arms)
- To determine the safety and tolerability of oral administration of olaparib alone and in combination of AZD1775, AZD5363, and AZD6738 in patients with advanced solid tumors
- To collect and store molecular profiling data of all patients enrolled in this study, for correlating treatment response/clinical benefit with patterns of tumor genetic abnormalities in tumors

1.3 Exploratory Objectives

- To correlate clinical benefit rate (CBR) associated with treatment at Week 16, Overall Response Rate (ORR), Complete Response (CR), and Partial Response (PR), with additional defects in DNA repair pathways measured by genetic aberrations in the tumors.
- To compare genetic variants/mutations measured in tumor tissue in diagnostic archival specimen, at baseline and on progression (when samples available), and correlate with tumor response and clinical benefit
- To determine tumor mutations in ctDNA at baseline, on treatment, and at progression, and evaluate the changes in ctDNA mutations and correlate with tumor response and clinical benefit

2 BACKGROUND

2.1 Background on cancer and molecular selection of patients

Over the last decade, the delineation of signaling pathways to understand tumor biology has laid the foundation for the discovery of novel targets and development of multiple therapies for cancer. The identification of driver mutations and critical pathway dependencies, as well as genomic sequencing and other large-scale “-omics” approaches, have facilitated the discovery and development of novel targeted anti-cancer therapeutics, or at least provide the scientific rationale

for their development. This increased molecular understanding of tumors has led to a new era of personalized medicine that has begun to influence common practice for oncologists beyond academic institutions.

Traditionally, the site of tumor origin, together with histology and clinical and/or pathological characteristics, especially stage, was used to make treatment decisions. This approach has been changed to include molecular tumor parameters. Markers presently used to guide decisions for personalized medicine treatment with targeted agents are either protein-based (immunohistochemistry (IHC)) or via detecting genetic aberrations. For genetic aberrations, a range of methodologies are used, nowadays often Next-Generation-Sequencing (NGS) of either multiple selected genes in parallel or whole exome sequencing, in particular in early clinical trials or for exploratory purposes. These large panels of genes offer the opportunity not only to detect aberrations, for which treatment options already exist, but also to generate data on additional driver mutations or resistance pathways [1,2]. Treatment decisions may be based on the data when tests have been performed in Clinical Laboratory Improvement Amendment (CLIA)-certified laboratories.

Molecular profiling, including genomic profiling, is rapidly becoming commonplace for cancer patients. As such, a growing number of patients are being identified with potentially actionable mutations, translocations or pathway activation events, without availability of matched targeted treatments. Multiple so-called "basket studies" are ongoing to investigate molecularly targeted agents, to explore if a similar molecular profile confers sensitivity to the same agents across tumor types.

Experience at our institutions and through published literature shows, however, that patients' tumors often bear multiple mutations and it is often not immediately obvious that one of these mutations would be the driving mutation. In addition, many targeted agents have shown efficacy, but are often more efficacious in combination with other anti-cancer treatments. The OLAPCO clinical trial therefore proposes to study combinations of agents in molecularly-defined patient populations across tumor types. Patients will be enrolled based on molecular profiling performed on tumor samples that has taken place prior to the study (the molecular profiling is not part of this study). The PARP inhibitor olaparib alone and combinations with olaparib will be tested based on the hypothesis that interfering with DNA damage repair in addition to targeting a specific signaling pathway by a second compound, would lead to increased cell death and tumor control.

2.2 DNA Damage Repair

DNA damage repair (DDR) is an essential function to maintain viability in all cells. Several specific, mutually supporting and overlapping mechanisms exist in eukaryotic cells to process the type of DNA damage that results from environmental and cellular stress. Base excision repair (BER) mediates the removal and replacement of single damaged bases. Nucleotide excision repair (NER), classically associated with UV damage, removes helix distortions with excision of a longer (27-29 bp) tract of DNA. Mismatch repair (MMR) excises mismatched DNA base pairs. DNA double strand breaks (DSB) can be repaired by either an error-prone process of non-homologous end joining (NHEJ) or homologous DNA recombination repair (HDR), an error-free process with the greatest repair fidelity and lowest frequency of errors. HDR is a mechanism to repair several DNA lesions, including DSBs, single-strand DNA breaks (SSBs) and interstrand crosslinks (ICL)[3].

Several types of DNA repair mechanisms of DSBs and SSBs converge on HDR. The occurrence of SSB and DSB is increased in cancer cells because of the higher frequency of DNA replication in mitotically active cancer cells, the increased frequency of DDR defects in cancer cells, and the generalized cancer phenotype of genomic instability.

PARP 1 and 2 (poly(ADP-ribose) polymerase) are nuclear proteins that act during the repair of SSBs, which are intermediates of base excision repair (BER)[4]. These catalyze the cleavage of NAD+ (nicotinamide adenine dinucleotide) and the formation of homopolymers of ADP-ribose on

chromatin and also on proteins. The homopolymers present on the DNA act to recruit enzymes that function in the repair of SSBs. Inhibition of PARP 1 and 2 blocks repair of the SSBs and leads to formation of DSBs as a result of replication fork collapse [5]. PARP attracts SSB repair proteins like XRCC1 to the site of DNA damage to catalyze the repair of strand breaks. PARP also has roles in B-NHEJ and the restart of stalled replication forks[3]. Thus, cells in which PARP 1 and 2 are inhibited rely on HDR to repair the DSBs. Inhibition of PARP activity in HDR-deficient BRCA mutant cells by genetic or pharmacological means is lethal and the magnitude of response is unprecedented[6,7]. Olaparib is a PARP1 & 2 inhibitor that demonstrates significant clinical activity in BRCA mutant breast and ovarian cancer [8, 9].

Recent work has identified a new class of genetic mutations that result in HDR defects not through disruption of DDR genes themselves but through epigenetic changes (A). The 2-Hydroxyglutarate (2HG) enantiomers, R-2HG and S-2HG are both 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. Recurring IDH1/2 mutations are found in gliomas and acute myeloid leukemia (AML), and in multiple other tumor types. Many IDH1/2-mutant tumors are known to be chemo- and radiosensitive, although the mechanisms underlying this enhanced sensitivity have yet to be explained.

Sulkowski et al (A) report that IDH1/2 mutations induce a homologous DNA recombination (HDR) defect which renders tumor cells exquisitely sensitive to Poly (ADP-Ribose) polymerase (PARP) inhibitors, including olaparib. This “BRCAness” phenotype can be completely reversed by small molecule mutant IDH1/2 inhibitors, and it can be entirely restored by treatment with either 2HG enantiomer in cells with intact IDH1/2. A detailed series of studies implicate two αKG-dependent dioxygenases, KDM4A and KDM4B, as key mediators of the observed HDR deficient repair phenotype. IDH1/2-dependent cells demonstrate olaparib and PARP inhibitor sensitivity in a range of clinically relevant models, including primary patient-derived glioma cells and AML bone marrow cultures *in vitro*, as well as genetically-matched tumor xenografts *in vivo*. These data indicate that the phenotype of 2HG-induced BRCAness is not tissue specific, suggesting that a diverse range of tumor types bearing these mutations can be exploited by PARP inhibitors. These observations have been extended to several structurally related and clinically relevant tricarboxylic acid (TCA) oncometabolites, such as fumarate and succinate, which demonstrate a marked synthetic lethality with olaparib/PARP inhibitors in tumors which produce these other oncometabolites, and the data suggest a similar mechanism of action via which HDR is suppressed. These findings uncover an unexpected link between oncometabolites, altered DNA repair and genetic instability but at the same time confer a collateral vulnerability to PARP inhibition that can be therapeutically exploited.

2.3 Background on targeted agents

2.3.1 Olaparib (AZD2281)

Olaparib (AZD2281, KU-0059436) is a potent inhibitor of polyadenosine 5’diphosphoribose polymerase (PARP)[10]. PARP inhibition is a novel approach to targeting tumors that have homologous recombination deoxyribonucleic acid (DNA) repair (HRR) pathway deficiencies (HDR). In HDR tumors, single agent treatment with olaparib can lead to tumor regression by a process known as synthetic lethality- a result of the accumulation of un-repaired DNA double-strand breaks (DSBs) and an unsupportable increase in genomic instability. Olaparib may also enhance the DNA damaging effects of ionizing radiation and chemotherapy. Within the clinical development program, the focus is to assess tolerability and efficacy of olaparib in patients with advanced solid tumors containing HDR, such as breast cancer susceptibility gene (BRCA-1, -2 and BRCAness) mutated cancers (germline and somatic).

Olaparib is currently being investigated in a range of Phase I, II, and III studies.

Further details are provided in B and the Investigators' Brochure.

2.3.2 AZD5363

AZD5363 is a potent, selective inhibitor of the kinase activity of the serine/threonine AKT/PKB that is being developed as a potential treatment for solid and hematological malignancies.

AKT is part of the AGC family of kinases (cAMP-dependent protein kinases A, cGMP dependent protein kinases G, and phospholipid-dependent protein kinases C). Mammalian cells express 3 closely related AKT isoforms: AKT1 (PKBα), AKT2 (PKBβ) and AKT3 (PKBγ), all encoded by different genes. AKT is involved in multiple signaling pathways promoting tumorigenesis, inhibiting apoptosis, impacting on the cell cycle and promoting invasion and migration.

The phosphatidylinositol 3-kinase (PI3K)/AKT/phosphatase and tensin homologue (PTEN) pathway is frequently deregulated in cancer and drives tumor growth and cell survival [15]. All 3 AKT isoforms are activated in different tumor types including breast, prostate, ovarian, pancreatic and gastric cancers. This activation is often associated with resistance to established cancer therapies as well as advanced disease and/or poor prognosis[16]. AKT activation in tumors is largely due to input from other signaling pathways upstream of AKT (e.g., mutation of oncogenes such as RAS, BCR-ABL, mutation of receptor tyrosine kinases such as epithelial growth factor receptor, amplification of human epidermal growth factor receptor 2 (HER2), loss of PTEN function, mutations of PI3K).

Inhibitors of AKT are anticipated to have efficacy when dosed in combination with cytotoxic chemotherapies or in combination with other targeted or anti-hormonal agents. AZD5363 inhibits all 3 AKT isoforms (AKT1, AKT2 and AKT3) and therefore has the potential to provide clinical benefit over a range of therapeutic indications.

A recent phase I study with olaparib and AZD5363 presented at AACR 2015 determined a RP2D for the combination. Dose escalation was completed in 7.5 months in 20 patients in 1 center; with ≥6 evaluable patients treated at each of the 3 dose levels in two different intermittent schedules of AZD5363. Common (>15%) G1-2 toxicities were nausea, vomiting, fatigue, diarrhea and anemia. A DLT of G3 rash was seen at 480mg BID AZD 4 of 7 days + 300mg BID Olaparib. Non DLT G3 anemia (n=2), diarrhea (n=2), fatigue (n=1) and vomiting (n=1) were seen in 4/7 arm; G3 hyperglycemia (n=1), transaminitis (n=1) and fatigue (n=2) in the AZD 5363 2 days of 7 arm. No significant PK interactions were seen. Intra-patient dose escalation of AZD5363 showed dose dependent increases in drug exposures. Platelet-rich plasma PD studies showed a significant decrease in pSer9 GSK3β post-therapy at all dose levels (mean ≥55% [p<0.002] in 4/7 arm and ≥70% [p<0.0001] in 2/7 arm). Confirmed partial responses were seen in a *BRCA* wild type *PTEN* LOH platinum resistant ovarian cancer patient for 6m and a *BRCA1* mutant ovarian cancer patient for 5.5m+. An unconfirmed PR was seen in a *BRCA1* mutated breast cancer patient (2.5m+ response duration). A *BRCA1* mutated castration resistant prostate cancer patient had a response (PSA 14 to 0.7 µg/L) and tumor response (8m+). A PI3K/mTOR inhibitor resistant peritoneal mesothelioma patient had stable disease for 9m+ with 66% CA125 decline (202 to 69 U/mL). The RP2C was established at 640mg BID 2/7 AZD5363 + 300mg BID Olaparib based on tolerability.

Phase I RP2D expansion and phase II trials with AZD5363 are ongoing.
Further details are provided in C and the Investigators' Brochure.

2.3.3 AZD1775 (MK1775)

AZD1775 is an inhibitor of *Wee*1, a protein tyrosine kinase. *Wee*1 phosphorylates and inhibits cyclin-dependent kinases 1 (CDK1) and 2 (CDK2), and is involved in regulation of the intra-S and G2 cell cycle checkpoints. Proper functioning of these checkpoints is essential for DNA metabolism and the DNA damage response [11].

CDK2 activity drives a cell into, and through, S-phase of the cell cycle where the genome is duplicated in preparation for cell division. CDK1 (also called cell division cycle 2, or CDC2) activity drives a cell from the G2 phase of the cell cycle into mitosis. In response to DNA damage, Wee1 inhibits CDK1 to prevent the cell from dividing until the damaged DNA is repaired (G2 checkpoint arrest). Inhibition of Wee1 is expected to release a tumor cell from chemotherapeutically-induced arrest of cell replication. Inhibition of Wee1 is expected to cause aberrantly high CDK2 activity in S-phase cells that, in turn, leads to unstable DNA replication structures and ultimately DNA damage.

It is anticipated that AZD1775 will have independent anti-tumor activity in the absence of added chemotherapy. *In vitro* experiments demonstrate that AZD1775 has synergistic cytotoxic effects when administered in combination with various DNA damaging agents with divergent mechanisms of action. Therefore, the primary objective of the clinical development of AZD1775 is its use as a chemosensitizing drug in combination with a cytotoxic agent (or combination of agents) for treatment of advanced solid tumors.

The tumor suppressor protein p53 regulates the G1 checkpoint. As the majority of human cancers harbor abnormalities in this pathway they become more dependent on S- and G2- phase checkpoints [12]. Thus, S- and G2-checkpoint abrogation caused by inhibition of Wee1 may selectively sensitize p53-deficient cells to anti-cancer agents [13]. In *in vitro* and *in vivo* preclinical models, AZD1775 selectively enhanced chemotherapy induced death of cells deficient in p53 signaling. Tumor context-specific sensitization to the DNA damaging agents gemcitabine and platinums was observed in TOV21G (ovarian carcinoma) cell lines matched for wild type and knock down of p53.

Data from a phase I monotherapy trial of AZD1775 in solid tumors presented at ASCO 2014 established the MTD at 225 mg bid for 5 doses/week, two out of every 3 weeks [14]. Toxicities were myelosuppression and diarrhea. PK exposure increased 2 to 3-fold on day 3 compared to day 1, with a half-life of 9-12 hours. Additionally, phosphorylated Tyr15-Cdk levels were shown in three of five paired tumor biopsies. One partial response (PR) was seen in a BRCA mutant patient with squamous cell carcinoma of the head and neck [14]. This study defined the MTD, toxicities, pharmacokinetics, and pharmacodynamics of AZD1775, and concluded that DDR mutations may confer sensitivity across tumor cell of origin types.

AZD1775 is currently tested in Phase I and Phase II clinical studies.

Further details are provided in the Investigators' Brochure. The AZD1775 plus olaparib arm will be added as an addendum to the protocol and opened once the recommended phase II dose is available.

2.3.4 AZD6738

AZD6738 is an inhibitor of the serine/threonine protein kinase Ataxia Telangiectasia and

Rad3 Related (ATR), a member of the phosphoinositide 3-kinase related kinase (PIKK) family. 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. ATR deletion is embryonic lethal in mice, however severe ATR hypomorphism is tolerated in humans leading to Seckel Syndrome. Normal cells from patients with Seckel Syndrome have reduced ATR function and show extensive DNA breaks when subjected to replication stress.

Ataxia Telangiectasia Mutated (ATM) is a closely related kinase that is recruited to double strand breaks and like ATR, has both checkpoint and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into double strand breaks through fork collapse and the resection of double strand breaks generates single stranded DNA. During tumorigenesis, ATM can be inactivated or lost providing a selection advantage for the tumor cell through the increased potential for genome alteration, and an increased dependence on ATR function. Similarly, oncogene activation such as that of c-Myc leads to increased replication stress, an accumulation of stalled replication forks and dependence on ATR function.

Sporadic ATM deficiency is reported in many malignant diseases (Stankovic et al 2002, Grønbæk et al 2002, Ambatipudi et al 2011, Bolt et al 2005, Mazumder et al 2011, Grabsch et al 2006), and ATM deficiency is expected to sensitize malignant cells to ATR inhibition through their complimentary roles in DNA damage repair. Patients with ATM deficient malignancies can be clinically identified and, in most cases, are known to have a poor prognosis with current therapies.

Although ATM-deficient cells have a greater sensitivity to AZD6738, AZD6738 is cytotoxic in cell line panels of ATM-proficient hematological malignancies *in vitro*. In vivo combinations of AZD6738 with radiation induces a dose-dependent anti-tumor response, with regressions in ATM-deficient models and growth inhibition in ATM-proficient models. Anti-tumor activity of AZD6738 may, therefore, also be seen more broadly.

There are other molecular features that could be envisaged to affect clinical response to ATR inhibition, and these would include: defects in additional genes/proteins that regulate ATM-function: MRE11A (NBS, RAD50 as part of M-R-N complex), TIP60 and CHK2; defects in G1/S checkpoint control (in addition to ATM/p53) and (ATR-dependent)

replicative stress. Molecular surrogates would be loss of tumor suppressors (e.g. CDKN2A/B (p15/p16) deletions) and/or coupled with hypoxia; and increased G1/S progression-proliferation and (ATR-dependent) replicative stress. Molecular surrogates would be oncogene driven and dependent tumors (e.g. Myc, Cyclin D/E, CDK4 amplified) and/or coupled with hypoxia.
The ATR-Chk1 checkpoint pathway serves to ensure cell survival after replication stress, therefore a normal and robust checkpoint is thought to be a mechanism of resistance to chemotherapy. As a result, ATR-Chk1 pathway components are considered promising therapeutic targets, and preclinical data generated to date supports this hypothesis (Mukhopadhyay et al 2005, Pan et al 2009, Powell et al 1995, Strunz et al 2002, Tao et al 2009, Parikh et al 2007).

Increasing the exogenous replication stress with approaches that generate DNA strand breaks or DNA lesions which stall DNA replication forks in the tumor cell, for example through radiation, chemotherapy or inhibition of other DNA repair proteins e.g. PARP, should also lead to increased sensitivity to ATR inhibition. Thus, UV radiation, cisplatin and hydroxyurea are more efficacious in tumor cells where kinase-dead ATR has been expressed, and over expression of a mutated form of ATR observed in Seckel cells increases their sensitivity to alkylating agents.

In patients with malignant disease, an ATR inhibitor has the potential to have monotherapy activity, through synthetic lethality (synthetic lethality arises when a combination of mutations in two or more genes, or inhibition of the production thereof, leads to cell death, whereas a mutation in only one of these genes does not, and by itself is said to be viable (Tucker and Fields 2003), e.g. ATM loss-of-function) or by exploiting on-going aberrant DNA replication. structures leading to dependency on ATR through replication stress (DNA replication stress is defined as inefficient DNA replication that causes DNA replication forks to progress slowly or stall (Burhans and Weinberger 2007)), to act synergistically in combination with DNA damaging radiotherapy, chemotherapy or novel DNA repair inhibitors such as ionising radiation, carboplatin or PARP inhibitors (e.g. olaparib) respectively which increase the threshold level of replication stress or induce DNA strand breaks; thus the potential for increased efficacy at the tumor with more manageable symptoms for normal tissues and to act as a maintenance therapeutic after either of the above

The AstraZeneca sponsored study D5330C0004 is investigating AZD6738 administered orally in combination with olaparib, in patients with advanced malignancies. 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). As of 1st June 2017, 64 patients have received treatment in Module 2, the RP2D has been established and patients with gastric cancer are being recruited to expansions in Parts B1 and B2. Amendment 8, which adds Parts B3 and B4 to the study, has been submitted to the regulatory authorities for approval.

Gr3-4 events occurring in ≥ 1 subject include anaemia, neutropenia, thrombocytopenia, ascites, anorexia, abdominal pain, large intestinal obstruction, leucopenia, dehydration and syncope. Very common adverse events (≥1/10 according to CIOMS III frequency classification) considered possibly related to AZD6738 and / or olaparib by the investigator include anaemia and fatigue. Common adverse events (≥1/1000 to <1/10) considered

possibly related, include nausea, neutropenia, thromobocytopenia, vomiting, anorexia, dizziness, diarrhoea, thrombocytopenia, leucopenia, increase in blood creatinine and asthenia.

A number of potential safety signals have been identified on the basis of general toxicology, safety pharmacology, genotoxicity and clinical studies. Most of these signals have not been confirmed to be causally related to AZD6738; some are considered potential risks which are being monitored in ongoing clinical trials e.g. gastrointestinal toxicity, hepatic toxicity, etc.; bone marrow toxicity is the only signal considered causally related to AZD6738, and is considered an ADR or identified risk for the product. In addition, some clinical toxicities from AZD6738 overlap with those seen with olaparib use in humans e.g. anemia, neutropenia, leukopenia, thrombocytopenia of potential prolonged duration.

The Recommended Phase 2 Dose for expansion has been declared as AZD6738 OD D1-7 with olaparib 300 mg BD continuously. The 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 IC_{90} threshold (based on ATR enzyme inhibition assay in LoVo cells) and the GI_{90} threshold (based on the cellular growth inhibition activity in LoVo cells) across the full dosing interval i.e 24 h. Please refer to AZD6738 IB 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 [71], 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.

In summary, 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. This compound 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. AZD6738 has the potential to provide benefit as a monotherapy or in combination with DNA damaging agents, including PARP inhibitors, in patients with both hematological and solid malignancies.

Further details are provided in the Investigators' Brochure. The AZD6738 plus olaparib

3 STUDY DESIGN AND RATIONALE

3.1 Description of Study

This is a phase II signal-searching study in a range of tumor types with the potential to identify novel tumor indications for combination therapy with olaparib that can subsequently be explored in dedicated studies. Patients will be enrolled in this study based on molecular

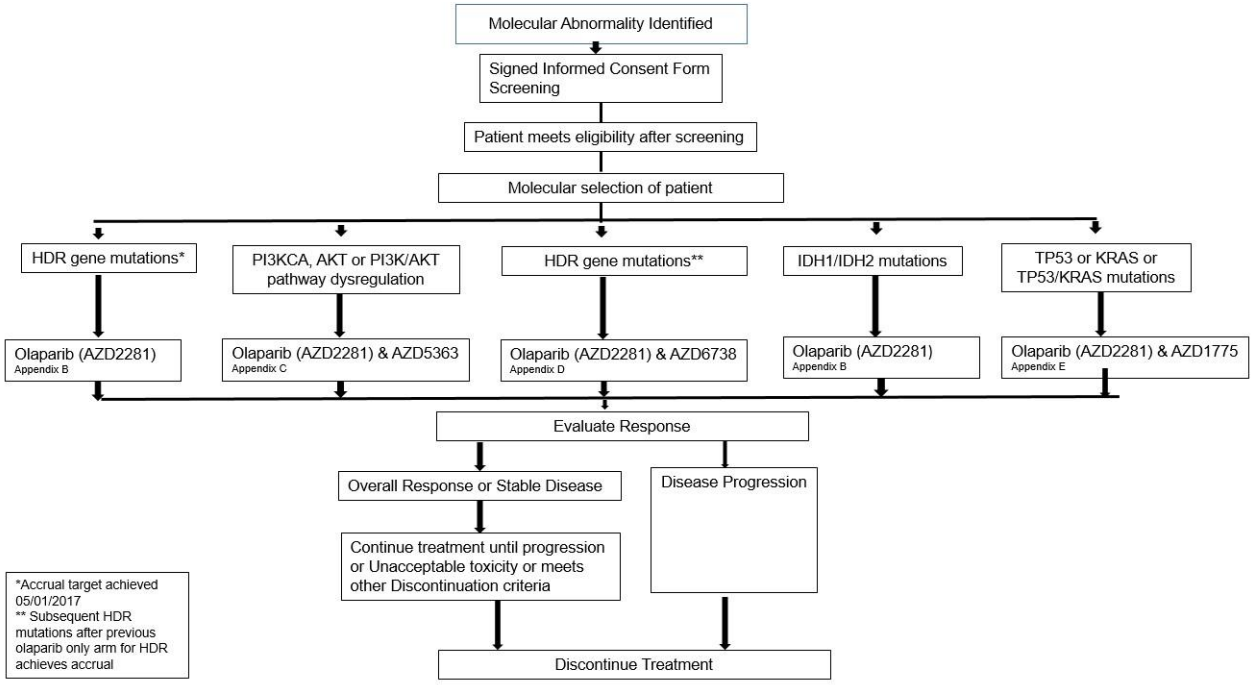
markers from genetic profiling performed on their tumors prior to study entry (outside of protocol). The trial will also identify genetic determinants of response and resistance.

Patients with tumors harboring mutations in DNA damage repair genes will be treated with olaparib and as accrual goals are achieved, olaparib and AZD6738. Patients with tumors harboring either *TP53* or *KRAS* mutations or mutations in *KRAS* and *TP53* will be treated with AZD1775 plus olaparib. Patients with tumors harboring *PIK3CA*, *AKT,* or *ARID1A* mutations or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway will be treated with AZD5363 plus olaparib. Patients with mutations in IDH1 or IDH2 will be treated with olaparib alone.

The recommended phase II dose of AZD1775 plus olaparib is not yet available. Phase I clinical trials are currently either under way to determine the recommended phase II doses for this combination. The AZD1775 plus olaparib will be added as an addendum to the protocol and opened once the recommended phase II doses are available.

For more detail on the molecular selection in the olaparib, AZD5363 plus olaparib and AZD6738 and olaparib treatment arms, please see Molecular selection of patients, B, C and D.

3.2 Main Study Schema



3.3 Rationale for combinations with olaparib

3.3.1 Combination of AZD1775 with Olaparib

TP53 mutations are one of the most common mutations across cancer types, but direct therapeutic targeting of p53 to restore the function of the tumor suppressor so far has had very limited success [22]. p53-deficient cells are more dependent on the S or G2 cell cycle checkpoint and may therefore, when treated with a G2 checkpoint inhibitor, be more sensitive to DNA damage [23, 24]. Inhibition of WEE1, a tyrosine kinase that phosphorylates CDK1 and thereby inactivates it, causes G2 checkpoint abrogation. AZD1775 (MK-1775) is a small molecule WEE1 inhibitor, that has been shown to sensitize p53-deficient tumor cells to DNA-damaging agents and radiotherapy [25-27]. In p53-deficient tumors, a combination of AZD1775 and the DNA-damage repair inhibitor olaparib may therefore be hypothesized to have synergistic anti-tumor efficacy. We are not aware of preclinical data combining AZD1775 and olaparib. However, WEE1 inhibition will lead to inappropriately high levels of CDK1 activation (and therefore checkpoint bypass). CDK1 can also phosphorylate BRCA2; this phosphorylation actually disrupts the interaction of BRCA2 and RAD51. Therefore, inappropriately high, unregulated CDK1 activity will reduce RAD51 loading and impair HR. Therefore, WEE1 inhibition should sensitize cells to PARP inhibition [28]. Mutant *KRAS* in cancer cells leads to hyperactivation of the Erk/p90RSK and PI3K/Akt pathways, and the phosphorylation of Chk1 at an inhibitory site. The resulting inhibition of ATR/Chk1 signaling abrogates the activation of the G2 DNA damage checkpoint and confers specific sensitization of mutant KRAS cancer cells to DNA damage [29]. Patients with KRAS mutations and mutations in *KRAS* and *TP53* will also be included in the study.

3.3.2 Combination of AZD5363 with Olaparib

AZD5363 is an AKT inhibitor, likely to be most active in patients with defects in the PI3K/PTEN pathway. PTEN-deficiencies, PIK3CA and AKT mutations are common events in multiple cancer types, with breast cancer as one of the examples with very high frequency, perhaps up to 50% in metastatic breast cancer [30].

Another PARP-inhibitor, BMN673, has shown anti-tumor activity in tumor xenografts that carried BRCA mutations or had PTEN- deficiency. Olaparib was used as a comparator and also showed efficacy in PTEN deficient cell lines [32]. A case report from a Phase I study using olaparib as monotherapy discussed a patient with a response to olaparib, who had a significant reduction in the size of brain metastases without steroid treatment or radiotherapy with patient-reported improvement. Upon progression after 8 months of treatment, the tumor biopsy displayed no somatic BRCA mutations, but showed PTEN loss [33].

Inhibition of the PI3K pathway by BKM120 in TNBC cell lines resulted in down regulation of BRCA and activation of PARP and sensitization to PARP inhibition by olaparib. The combination of both agents was more efficacious in some TNBC xenografts than each agent alone. These data therefore generated a rationale for combination of olaparib with PI3K inhibitors outside of the gBRCA setting and based on these data a clinical study combining olaparib with BKM120 is ongoing [34]. Synergy of the PI3K inhibitor with olaparib was also reported in the MMTV breast cancer model and two human BRCA1-related breast cancer models, suggesting that combined PI3K and PARP inhibition may be an effective treatment in certain breast cancers [35]. A recent PhI study reported at ASCO 2014 that combining olaparib with BKM120 was feasible with evidence of clinical benefit at all evaluated doselevels [36]. Therefore, combinations with an AKT- inhibitor, targeting the same

signaling pathway may also be effective.

Increased AKT phosphorylation has been shown to occur in tumors with ARID1A deficiency and these tumors have been shown to be sensitive to treatment with the AKT inhibitor MK-2206 [37-39] Patients with ARID1A mutations can therefore be included in the AZD5363 plus olaparib combination arm.

3.3.3 Combination of AZD6738 and Olaparib

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. ATR deletion is embryonic lethal in mice, however severe ATR hypomorphism is tolerated in humans leading to Seckel Syndrome. Normal cells from patients with Seckel Syndrome have reduced ATR function and show extensive DNA breaks when subjected to replication stress.

Ataxia Telangiectasia Mutated (ATM) is a closely related kinase that is recruited to double strand breaks and like ATR, has both checkpoint and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into double strand breaks through fork collapse and the resection of double strand breaks generates single stranded DNA. During tumorigenesis, ATM can be inactivated or lost providing a selection advantage for the tumor cell through the increased potential for genome alteration, and an increased dependence on ATR function. Similarly, oncogene activation such as that of c-Myc leads to increased replication stress, an accumulation of stalled replication forks and dependence on ATR function.

Sporadic ATM deficiency is reported in many malignant diseases (Stankovic et al 2002, Grønbæk et al 2002, Ambatipudi et al 2011, Bolt et al 2005, Mazumder et al 2011, Grabsch et al 2006), and ATM deficiency is expected to sensitize malignant cells to ATR inhibition through their complimentary roles in DNA damage repair. Patients with ATM deficient malignancies can be clinically identified and, in most cases, are known to have a poor prognosis with current therapies.

Although ATM-deficient cells have a greater sensitivity to AZD6738, AZD6738 is cytotoxic in cell line panels of ATM-proficient hematological malignancies *in vitro*. In vivo combinations of AZD6738 with radiation induces a dose-dependent anti-tumor response, with regressions in ATM-deficient models and growth inhibition in ATM-proficient models. Anti-tumor activity of AZD6738 may, therefore, also be seen more broadly.

There are other molecular features that could be envisaged to affect clinical response to ATR inhibition, and these would include: defects in additional genes/proteins that regulate ATM-function: MRE11A (NBS, RAD50 as part of M-R-N complex), TIP60 and CHK2; defects in G1/S checkpoint control (in addition to ATM/p53) and (ATR-dependent) replicative stress. Molecular surrogates would be loss of tumor suppressors (e.g. CDKN2A/B (p15/ p16) deletions) and/or coupled with hypoxia; and increased G1/S progression-proliferation and (ATR-dependent) replicative stress. Molecular surrogates would be oncogene driven and dependent tumors (e.g. Myc, Cyclin D/E, CDK4 amplified) and/or coupled with hypoxia.

The combination of AZD6738 and olaparib are synergistically cytotoxic in HDR ovarian cancer cell lines in vitro and in vivo in a BRCA2$^{-/-}$ PDX model. PARP inhibition activates ATR/CHK1 as a survival mechanism and concurrent inhibition of this pathway permits the BRCA $^{-/-}$ cells to enter into mitotic catastrophe and apoptosis (B). The ATR-Chk1 checkpoint pathway serves to ensure cell survival after replication stress of many types, therefore a normal and robust checkpoint is thought to be a mechanism of resistance to chemotherapy.

3.4 Molecular Selection of Patients

Patients with appropriate tumor profiles will be consented for enrollment in a specific arm of the clinical study prior to screening for further eligibility.

Mutations, translocations, amplifications or other pathway activations inhibited by the listed agents will be identified by tests performed in a CLIA-certified laboratory, either locally, at one of the other participating sites or at a commercial testing facility, prior to participation in the trial. This process will not formally be part of this clinical protocol.

Patients will be selected and treated as follows:

a. Patients with tumors harboring mutations in HDR genes will be treated with olaparib.
b. Patients with tumors harboring *P T E N* , *PIK3CA*, *AKT,* or *ARID1A* mutations or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway will be treated with AZD5363 plus olaparib.
c. Patients with tumors harboring either *TP53* or *KRAS* mutations or mutations in *KRAS* and *TP53* will be treated with AZD1775 plus olaparib. *TP53* mutations must be found on the *TP53* mutation eligibility list.
d. Patients with tumors harboring mutations in HDR genes, including ATM, CHK2, APOBEC, MRE11 complex, will be treated with AZD6738 and olaparib. The apparent overlap between the olaparib alone and the AZD6738 plus olaparib is not present since accrual to the olaparib alone arm will be completed prior to accrual to olaparib and AZD6738 arm.
e. Patients with cholangiocarcinoma harboring IDH 1/ 2 tumors will be treated with olaparib.

If a patient's tumor is found to have multiple mutations (*TP53* and *PIK3CA*, for example) meeting criteria for multiple arms, the decision of which arm to enroll the patient should be made by the treating physician. These decisions should also be made in conjunction with the Study PI.

For details on patient selection specific to the study drugs to be used please see the following appendices:

- Olaparib (B)
- AZD5363 plus Olaparib C)
- AZD6738 plus Olaparib (D).

4 PATIENT SELECTION

4.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically documented metastatic cancer (solid tumors, not including hematologic malignancies)
- Patients who have received standard first-line therapy for metastatic cancer (except for the tumors for which no first-line therapy exists) and in whom a trial of targeted therapy is considered the best available treatment option. Eligible patients should not have available

therapies that will convey clinical benefit.

- Progressive cancer at the time of study entry
- Measurable disease by RECIST v1.1
- Age ≥ 18 years
- Life expectancy ≥ 16 weeks
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 (APPENDIX A: Performance Status Criteria)
- Able to understand the nature of this trial and provide written informed consent
- Patient is 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.
- Molecular testing or appropriate IHC results from CLIA-certified laboratories used for patient eligibility should be obtained from the most recent tumor biopsy (baseline tumor biopsies and on-progression tumor biopsies are optional)
- No previous treatment with olaparib or any other drug sharing the same target. Prior treatment with PARP inhibitor monotherapy is allowed in the combination arms.
- Prior radiation therapy is allowed. Patients must not have received radiation therapy within 21 days prior to the initiation of study treatment.
- Other therapies: Prior experimental (non-FDA approved) therapies and immunotherapies are allowed. Patients must not have received these therapies for 21 days or five half-lives of the drug (whichever is less) prior to the initiation of study treatment and must have full recovery from any acute clinically significant effects of these therapies.
- Adequate hematologic function defined as:
  - Absolute neutrophil count (ANC) ≥ 1500/μL
  - White blood cells (WBC) > 3 x10^9/L
  - Hemoglobin (Hgb) ≥ 10 g/dL (may be achieved with erythropoietin agents; no blood transfusions in the 28 days prior to entry)
  - Platelets ≥ 100,000/μL
  - No features suggestive of MDS/AML on peripheral blood smear
- Adequate renal and liver function defined as:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × the upper limit of normal (ULN) (≤ 5 × ULN if considered due to primary or metastatic liver involvement)
  - Total bilirubin ≤ 1.5 ×ULN' Alkaline phosphatase ≤ 2× ULN (≤ 5 × ULN if considered due to tumor)
  - Serum creatinine ≤ 1.5 ULN
- 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 calipers by clinical exam

  OR

  At least one lesion (measurable and/or non-measurable) that can be accurately assessed by CT/MRI/plain x-ray/clinical exam at baseline and follow up visits.
- Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 28 days prior to starting the study drug. Both males and females must agree to adequate birth control if conception is possible during the study and for 6 months after the last dose. Female patients are considered to not be of child-bearing potential if they have a history of tubal ligation or hysterectomy or are post-menopausal with a minimum of 1 year without menses.

Additional inclusion criteria specific to the study drug to be used are as follows:

- Olaparib → Olaparib and AZD6738
  - Patients with solid tumors that harbor homologous DNA repair (HDR) gene mutations as exemplified below detected by next-generation sequencing (NGS) or real-time-polymerase chain reaction (RT-PCR) in assays performed at a Clinical Laboratory Improvement Amendments (CLIA)- certified laboratory:
    - Examples of Homologous DNA repair deficiency/HDR (germline/somatic mutations in tumors), but not limited to, are: BRCA 1, BRCA2/FANCD1, PALB2, RAD51, RAD 52, FANCN, FANCJ, FANCD2, DSS1, FANCC1, MRE11, RAD50, NSB1, BLM, ATM, ATR, CHK1, CHK2, FANC A,-B,-C, -E, -F, -G,-L, M, D2
- AZD5363 plus Olaparib
  - Patients with solid tumors with *PIK3CA* or *AKT* mutations or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway detected by next-generation sequencing (NGS) or real-time-polymerase chain reaction (RT-PCR) in assays performed at a Clinical Laboratory Improvement Amendments (CLIA)- certified laboratory:
    - activating mutations in *PIK3CA, AKT1, AKT2, AKT3, ARID1A;*
    - other molecular aberrations leading to dysregulation of the PI3K/AKT pathway, for example *PIK3R1and PTEN;*
    - if new information emerges relating to molecular aberrations that dysregulate the PI3K/AKT pathway, patients whose tumors bear these aberrations can be included in the study.
- Olaparib for neomorphic oncometabolites, such as 2-HG, in patients harboring mutations in IDH1/IDH2 mutant tumors or TCA/tricarboxylic acid cycle mutations such as FH and/or SDH.
- The AZD1775 plus Olaparib additional inclusion criteria will be added as an addendum to the protocol and opened once the recommended phase II doses are available.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Patients with known germline BRCA mutations in breast cancers will be excluded from the study, however testing is not required for inclusion in the study.
- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
- Prior standard of care cancer chemotherapy, immunotherapy or radiotherapy < 21 days prior to first dose of study agent(s).
- Patients with hematologic malignancies (includes patients with myelodysplastic syndrome/ acute myeloid leukemia).
- Patients with primary CNS malignancies
- Patients must not have received allogeneic stem cell transplant
- Concurrent administration of any other anti-cancer therapy
  - Bisphosphonates and Denosumab for bone metastases are allowed if started at least 4 weeks prior to treatment with study agent(s).
  - Octreotide is allowed if dose is stable for >3 months with no worsening of carcinoid syndrome
  - Hormonal therapy with luteinizing hormone-releasing hormone (LHRH) analogues for medical castration in patients with castrate-resistant prostate cancer is permitted
- Patients who have not demonstrated stable recovery (28 days or greater) from ≤ CTCAE grade 2 non-hematological toxicities related to prior therapy, such as peripheral neuropathy or alopecia, or incomplete recovery from previous surgery, unless agreed by the Principal Investigator (PI) and documented, are not eligible to participate in this study.
- Active or untreated brain metastases or spinal cord compression
  - A scan to confirm the absence of brain metastases is not required.

- Patients with treated brain metastases or spinal cord compression are eligible if they have minimal neurologic symptoms and evidence of stable disease (for at least 1 month) or response on follow-up scan. The patient can receive a stable dose of corticosteroids before and during the study if started at least 28 days prior to initiating the study agent(s).

- History of carcinomatous meningitis
- Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated stage I cancers (cervix, breast, colon, lung or prostate as examples) or other advanced (> Stage I) solid tumors curatively treated with no evidence of disease for ≥ 5 years.
- Patient must not have a co-morbid condition(s) that, in the opinion of the investigator, prevent safe treatment.
- Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy (testing is not part of the protocol).
- Patients with known (testing is not part of the protocol) active hepatic disease (i.e., Hepatitis B or C) due to risk of drug interactions with anti-viral therapy.
- Any of the following cardiovascular events within 6 months prior to study entry: myocardial infarction, malignant hypertension, severe/unstable angina, symptomatic congestive heart failure, cerebral vascular accident, or transient ischemic attack
- History or presence of clinically significant ventricular or atrial dysrhythmia > Grade 2 (NCI CTCAE v4.0)
  - Patients with chronic, rate-controlled atrial arrhythmias who do not have other cardiac abnormalities are eligible.
- Major surgery within 3 weeks prior to first dose of study treatment, and patients must have recovered from the effects of surgery
- Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication
- Refractory nausea and vomiting, chronic gastrointestinal diseases (e.g. inflammatory bowel disease) or significant bowel resection that would preclude adequate absorption
- Patients with uncontrolled seizures
- Inadequate bone marrow reserve within past 28 days prior to study treatment, excluding clinically documented therapy related toxicity that have recovered at time of screening, as exemplified by:
  - Absolute neutrophil count (ANC) < 1500/µl,
  - WBC ≤ 3 x 10^9/L
  - Platelet count (PLT) < 100,000/µl, or
  - Hemoglobin (Hgb) < 10 g/dL
- Blood (packed red blood cells, platelets) transfusions within 1 month prior to study start
- Whole blood transfusion in the last 120 days prior to entry to the study
- Patients with concomitant use of drugs, herbal supplements and/or ingestion of foods known to strongly modulate CYP3A4 enzyme activity as specified in the drug specific appendix.
- Women who are pregnant or lactating (breastfeeding)
- Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
- Patients with a known hypersensitivity to the combination/comparator agent
- Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results
  - 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, superior vena cava

syndrome, extensive bilateral lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent

- Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol

All patients must also meet the specific criteria for individual study drugs as follows:

- Olaparib
  - No additional exclusion criteria

- AZD5363 plus olaparib
  - Clinically significant abnormalities of glucose metabolism as defined by any of the following:
    - Diabetes mellitus type I- Fasting plasma glucose [fasting is defined as no calorific intake for at least 8 hours]: ≥ 7.0mmol/L (126 mg/dL) for those patients without a pre-existing diagnosis of Type 2 diabetes mellitus≥ 9.3 mmol/L (167mg/dL) for those patients with a pre-existing diagnosis of Type 2 diabetes mellitus
    - Glycosylated hemoglobin (HbA1C) ≥ 8.0% (63.9 mmol/mol)
    - Requirement for insulin for routine diabetic management and control
  - Requirement for more than two oral hypoglycemic medications for routine diabetic Patient must have no evidence of clinically significant troponin elevation (any CTC grade)
  - Patient must not have ≥ Stage II NYHA classification cardiac status; recent history (i.e., within 6 months) of coronary artery disease or arteriosclerotic cardiovascular disease (angina, myocardial infarction [MI])
  - Patient must not have PR interval greater than 200 msec
  - Patient must not have clinically significant PR (PQ) interval prolongation
  - Patient must not have resting LVEF < 55% measured by echocardiogram or MUGA, regional wall abnormality on ECHO, or any clinically significant structural abnormalities on echocardiogram such as left ventricular hypertrophy or diastolic dysfunction or valvular disease
  - Patient must not have QTcF > 480 msec or b) family history of long QT Syndrome or c) evidence of recent myocardial infarction e.g. within 6 months prior to start of study treatment) or risk of having a re-infarction, or d) history of torsade de pointes or e) QTcF < 350 msec (short QT syndrome)
  - Patient must not have intermittent second or third-degree AV block (Second degree AV block (Mobitz Type I and II). Third Degree AV block (Complete Heart Block). Incomplete, full or intermittent bundle branch block (QRS 110-120ms with normal QRS and T wave morphology is permitted if there is no evidence of left ventricular hypertrophy. Mobitz type 1, Wenckebach while asleep is permitted
  - Patient must not have clinically significant abnormalities in T wave or ST-T changes that can be indicative or be suggestive of acute ischemic changes or acute injury pattern
  - Use of any of the following potent negative inotropic drugs:
    - calcium channel blockers: verapamil or diltiazem; beta-blockers (pending discussion with cardiac SKG): metoprolol, propranolol, atenolol, bisoprolol, carvedilol, timolol, sotalol, esmolol; anti- arrhythmics (Class I): disopyramide, procainamide, mexiletine; (Class III): amiodarone
  - patients with uncontrolled hypotension (systolic blood pressure <90 mmHg and/or diastolic blood pressure <50 mmHg)
  - Patients with potassium or sodium levels outside the normal range for the site

- Patients with proteinuria (3+ on dipstick analysis or >500 mg/24 hours)

- AZD6738 plus olaparib
  - A diagnosis of ataxia telangiectasia
  - Receiving, or having received during the four weeks prior to first dose, corticosteroids (at a dose > 10 mg prednisolone / day or equivalent) for any reasons
  - Intestinal obstruction or CTCAE grade 3 or grade 4 upper GI bleeding within 4 weeks before the dosing
  - Treatment with any biological IMP e.g. immune check point blockers, antibodies, nanoparticles, experimental) within 42 days prior to the first dose
  - Known hypersensitivity to AZD6738 or any excipient of the product
  - Patients with myelodysplastic syndrome / acute myeloid leukemia or with features suggestive of MDS / AML
  - Patient must not have impaired hepatic or renal function as demonstrated by the following laboratory value, in addition to those values previously delineated:
    - Total bilirubin > 1.5 ×ULN (or likely to be in 3 weeks)
    - AST or ALT > 2.5 ULN (unless lever metastases are present in which case they must be > 5x ULN)
    - Albumin < 33 g/L (or outside of local laboratory reference range)
    - INR ≥ 1.5 or other evidence of impaired hepatic synthesis function
    - Alkaline phosphatase > 2.5 ×ULN (≤ 5 × ULN if considered due to tumor)
    - Serum creatinine > 1.5 ULN
    - Glomerular filtration rate (GFR) < 51 mL/min, as assessed using the standard methodology at the investigating center (e.g. Cockcroft-Gault, MDRD or CKD-EPI formulae, EDTA clearance or 24 hr urine collection)
    - Hematuria: +++ on microscopy or dipstick
  - Patient must not have > Class II NYHA classification cardiac status, recent history (i.e., within 6 months) of coronary artery disease or arteriosclerotic cardiovascular disease (unstable angina, myocardial infarction), or unstable cardiac arrhythmias
  - Patient must not have resting LVEF < 55% measured by ECHO/MUGA
  - Patient must not have mean resting corrected QT interval (QTc) >470 msec obtained from 3 electrocardiograms (ECGs) in 24 hours using the Fredericia formula.
  - Patient must not have any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block).
  - Patient must not have any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age.
  - Patient must not be at risk of brain perfusion problems, e.g., carotid stenosis
  - Patients with relative hypotension (< 100/60 mm Hg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of >20mm Hg.
  - Patient must not have uncontrolled hypertension requiring clinical intervention.
  - Subjects receiving, or having received, concomitant medications, herbal supplements and/or foods that strongly modulate CYP3A4 or P-glycoprotein activity (wash out periods of two weeks, but three weeks for St. John's Wort).
  - Concomitant use of known strong CYP3A4 inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevit) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks.

- Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g. 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.

- The AZD1775 plus olaparib additional exclusion criteria will be added as an addendum to the protocol and opened once the recommended phase II doses are available.

5 REGISTRATION PROCEDURES

5.1 General Guidelines

Eligible patients will be entered on study centrally at Yale (YCCI). Prior to obtaining signed informed consent from a patient, the site principal investigator or designee must contact the YCCI Project Manager to inquire about study slot availability. If available, the potential study participant will be consented and all required screening procedures will be completed, as outlined in the appendices for each treatment arm. The site principal investigator (or other approved investigator) must document that the participant has met all inclusion/exclusion criteria.

Following completion of eligibility testing, the participating site must provide documentation verifying eligibility of the patient to the YCCI Project Manager (refer to Study Procedure Manual for acceptable documentation). Upon review and approval by the YCCI Project Manager, the patient will be registered into Yale's web-based clinical database (OnCore). Confirmation of registration and treatment arm, in addition to a unique patient ID number, will then be communicated to the participating site.

Following registration, patients should begin protocol treatment within 72 hours (if a spot is available). Issues that would cause treatment delays should be discussed with the Study Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The YCCI Project Manager should be notified of cancellations as soon as possible.

5.2 Registration Process

Detailed information regarding the patient registration process is located in the Study Procedure Manual.

6 TREATMENT PLAN

6.1 Agent Administration

Dose Schedule		
Drug Combination	Dose* ***Olaparib***	***Combination Drug***
Olaparib	300mg BID	None
Olaparib + AZD5363	300mg BID	640mg BID D1-2/weekly
Olaparib + AZD6738	300mg BID	160 mg daily D1-7/Q 28 D

Olaparib + AZD1775**	300mg BID	TBD
Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage.* * The AZD1775 plus olaparib arm doses will be added as an addendum to the protocol once the recommended phase II doses are available.*		

Please refer to the appendices for the specifics of agent administration for each agent as follows:

- Olaparib (B)
- AZD5363 plus olaparib (C)
  - AZD6738 plus olaparib (D)
  - The AZD1775 plus olaparib arm agent administration will be added as an addendum to the protocol once the recommended phase II doses are available.

6.2 Definition of Toxicity

If toxicities occur, they will be defined based on toxicities observed following the administration of olaparib or the combination administration (C1D1) of olaparib and AZD1775, AZD5363, and AZD6738. Toxicities will be graded using the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the following web site: (http://ctep.cancer.gov).

Management and dose modifications associated with the above adverse events are outlined In the following appendices:

- Olaparib (B)
- AZD5363 plus olaparib (C)
- AZD6738 plus olaparib (D)
- The AZD1775 plus olaparib arm agent administration will be added as an addendum to the protocol once the recommended phase II doses are available.

Assessment of tumor response will be performed at 8 week intervals. Assessment for full expansion from 16 to 25 patients will be made at 16 weeks. Patients with an objective response or stable disease may receive additional treatment cycles until disease progression or withdrawal criteria are met. Ongoing evaluation of response will be conducted every 8 weeks, and safety will be evaluated weekly.

Other Modalities or Procedures

- Olaparib (B)
- AZD5363 plus olaparib (C)
- AZD6738 plus olaparib (D)

6.3 Concomitant and Excluded Therapies

6.3.1 Permitted Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient from ≤ 7 days prior to the first dose of study drug to the end of treatment visit. All concomitant medications should be reported to the investigator.

Patients who use oral contraceptives or hormone-replacement therapy and do not have breast cancer may continue these medications under the supervision of their physician. Other medications may be continued unless otherwise indicated in the specific study drug

appendix.

Supportive care, including certain antiemetic medications, may be administered at the discretion of the investigator unless otherwise indicated in the specific study drug appendix.

6.4 Prohibited Therapy

No other investigational therapy should be given to patients.

No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial.

- Bisphosphonates and Denosumab for bone metastases are allowed as long as these were started at least 4 weeks prior to treatment with study drug.
- Octreotide is allowed if dose is stable for >3 months with no worsening of carcinoid syndrome.
- Hormonal therapy with luteinizing hormone-releasing hormone (LHRH) analogues for medical castration in patients with castrate-resistant prostate cancer is permitted.
- Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present. Study treatment should be discontinued for a minimum of 3 days before the patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks if bone marrow toxicity has resolved.

Additional excluded concomitant therapies are provided in the specific appendix for each study drug:

- Olaparib (B)
- AZD5363 plus olaparib (C)
- AZD6738 plus olaparib (D)
- The AZD1775 plus olaparib arm agent administration will be added as an addendum to the protocol once the recommended phase II doses are available.

6.5 Duration of Therapy

In the absence of significant treatment delays ≥4 weeks due to adverse events determined to be probably/definitely attributed to a study agent (as defined in Adverse Events Characteristics), treatment may continue indefinitely or until one of the following criteria applies:

- Objective disease progression according to RECIST criteria
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) to include any drug toxicity considered related, probably related, or possibly related to the drug. This excludes only toxicities clearly not related to the drug, such as environmental, unrelated trauma, etc.
- Severe non-compliance to study protocol as judged by the investigator
- Patient becomes pregnant
- Patient is determined to no longer meet the required inclusion/exclusion criteria for the study
- Patient decides to withdraw from the study (the subject is at any time free to discontinue treatment, without prejudice to further treatment)
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

6.6 Duration of Follow Up

Patients will be followed for 30 days after removal from study or until death, whichever occurs first. Patients will be followed every 12 weeks (+/- 1 week) thereafter by phone for survival status. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.7 Criteria for Removal from Study

Patients will be removed from study when appropriate criteria listed in Section 6 applies. The reason for study removal and the date the patient was removed must be recorded.

7 DOSING DELAYS / MODIFICATIONS / DISCONTINUATION

Toxicities will be graded using the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the following web site: (http://ctep.cancer.gov).

- Doses of olaparib and AZD5363 will be administered at the same dose level throughout a cycle if no toxicities occur
- If a toxicity is < Grade 3, the patient can continue the daily dosing at the same dose level if the principal investigator deems it safe to proceed after evaluation of the toxicity
- If an intolerable Grade 2 toxicity or Grade 3 or 4 toxicity is observed at any time during a treatment cycle, the dose olaparib and/or AZD5363 for subsequent cycles will be reduced to the next lower dose level as discussed in the following appendices:
  - Olaparib (APPENDIX B)
  - AZD5363 plus olaparib (APPENDIX C)
  - AZD6738 plus olaparib (APPENDIX D)
  - The AZD1775 plus olaparib arm dosing delays/modifications/discontinuation will be added as an addendum to the protocol once the recommended phase II doses are available.
- All dose modifications will be based on toxicities that are determined to be definite/probably or unlikely/unrelated attributed to a study agent (as defined in Adverse Events Characteristics) and not attributable to disease or other causes.

The combination of olaparib and/or AZD5363 and/or AZD6738 will be treated as separate entities and any dose modification will occur as indicated in APPENDICES C and D. The AZD1775 plus olaparib arm will be added as an addendum to the protocol once the recommended phase II doses are available.

If there is a < 4 week delay due to recovery of toxicity or if there is a report of grade 3 or grade 4 toxicity thought to be due to olaparib and/or AZD5363 or AZD6738 therapy, then the patient will be re-treated at the specified dose modification.

A new cycle of therapy should not begin until the treatment-related toxicity has recovered to baseline grade if baseline was grade 2 or NCI-CTCAE grade 1 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If there is a ≥ 4 week delay of treatment due to drug-related toxicity, then the patient will discontinue the combination therapy and be removed from the study. The patient may continue to receive this investigative combination until any criteria defined in Duration of Therapy applies. Dose reductions may occur multiple times; as long as the participant continues to respond to therapy, reductions may occur down to the lowest protocol-specified dose level. Dose re-escalation will not be allowed. Every effort will be made to follow patients to progression/death regardless of future treatment once study treatment is discontinued and they are removed from the study.

An exception to the management of treatment-related toxicity is the occurrence of leukopenia and/or anemia. In this case, the AE should be managed as deemed appropriate by the investigator (growth factor, transfusions), without interruption in study drug or change in dose. However, growth factors must be discontinued once the AE has recovered to grade 1 or better. They may be resumed if leukopenia/anemia develops again. Treatment should be stopped before surgery and re-started following recovery. No stoppage of treatment is required for any biopsy procedures. Treatment should be discontinued for a minimum of 7 days before a patient undergoes therapeutic radiation treatment. This is not required where palliative doses are used.

Any patient discontinuing investigational product should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule or contacted at least 30 days after discontinuing study medication to collect and /or complete AE information. The patient's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment.

After discontinuation of the study medication at any point, all ongoing or new (within 30 days after discontinuation) AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up.

8 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

8.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are listed below. Toxicities will be graded using the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the following web site: (http://ctep.cancer.gov).

Adverse event
An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

Serious adverse event
A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs. Based on the expert's judgment, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such.

Other Significant Adverse Events (OAE)
OAEs will be identified by the Drug Safety Physician and if applicable also by the Study Team Physician during the evaluation of safety data for the CSR. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are AEs of reduction in ejection fraction, marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the CSR.

8.2 Recording of adverse events

Non-serious adverse events and SAEs will be collected from the time the study drug is given, throughout the treatment period and up to and including the *30 day follow-up* period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 30 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs they must be reported to the FDA and AstraZeneca per Reporting to the Food and Drug Administration and Reporting to AstraZeneca (AZ). SAEs determined to be related to study treatment occurring after the 30 day follow-up period must also be reported.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (definite/probably or unlikely/unrelated) and comparator/combination drug (definite/probably or unlikely/unrelated)
- Action taken with regard to investigational product/comparator/combination agent
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Definitions. An AE of severe intensity need not

necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

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.

Adverse Events based on examinations and tests
Deterioration as compared to baseline in protocol-mandated parameters (eg laboratory values) 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 parameter 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).

Deterioration of a parameter, 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 ≥3x ULN **or** total bilirubin ≥ 2x ULN may need to be reported as SAEs, please refer to G 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

New cancers
The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 8.1). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

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**. 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 AstraZeneca within the usual timeframes.

8.3 Follow-up of unresolved adverse events

All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

8.4 Causality collection

The causality of SAEs (their relationship to all study treatment) will be assessed by the investigators and communicated to the FDA, AstraZeneca, and appropriate IRBs.

8.5 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to cancer. It may be an increase in the severity of the cancer or an increase in the symptoms of the disease. Expected progression of the disease under study and /or expected progression of signs and symptoms of the disease under study, unless more severe in intensity or more frequent than expected for the patient's condition should not be reported as an AE. The development of progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression must not be reported as an AE/SAE.

8.6 Lack of Effect

Where 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, disease progression or constitutes an AE. In such cases, unless the reporting physician considers that the study treatment contributed to the deterioration or local regulations state to the contrary, the deterioration should be considered to be lack of efficacy and not an AE.

8.7 Adverse Events 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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the following web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment
- Probable – The AE *is likely 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

8.8 Yale Principal Investigator Safety Reporting Requirements

AEs classified as "serious" and "unexpected" that are probably/definitely attributed to drug administration, or SAEs whose frequency exceeds expectations, require expeditious handling and reporting.

The PIs will promptly investigate all safety information related to an adverse experience. If the results of the PIs' investigation show an adverse drug experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with drug

administration) is so reportable, the PIs will report such experience. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

All adverse events will be reported to AstraZeneca at the conclusion of the study.

8.8.1 Reporting to the Yale Human Investigation Committee

All SAEs, whether originating at Yale or a collaborating center, meeting the criteria for prompt reporting will be reported to the Yale University Human Investigation Committee (HIC) as per Yale HRPP policy.

The Yale University Human Investigation Committee prompt reporting criteria are: Unexpected (in terms of nature, specificity, severity, or frequency) AND related or possibly related to participation in the research AND the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

8.8.2 Reporting to the Food and Drug Administration

This study will be conducted under an IND (Investigational New Drug application) that will be held by the PI. The Principal Investigator will report in an expedited manner all SAEs meeting the criteria of "serious", "unexpected" and "related to study treatment". Written safety reports will use a MedWatch Form 3500A. A "fillable pdf" version with instructions is available at:http://www.fda.gov/medwatch/safety/FDA-3500A_Fillable_08-16-2006.pdf

There are two types of expedited safety reports to the FDA:

1. **7-Calendar-Day FDA Telephone or Fax Report:** The sponsor-investigator will directly notify the FDA, within 7 calendar days after his initial receipt of the information, of any adverse event that is ALL of the following:

Death or immediately life-threatening
Unexpected
Associated with the use of the study drug

Notification to the FDA will be made directly to the new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever was responsible for the review of the IND.

A written report of the event is to follow within 15 calendar days.

2. **15-Calendar-Day FDA Written Report:** The sponsor-investigator will directly notify the FDA within 15 calendar days of any adverse event that is ALL of the following:

Serious (due to non-fatal and non-life threatening criteria
Unexpected
Associated with the use of the study drug

Note: Serious Adverse Events which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

8.8.3 Reporting to AstraZeneca (AZ)

Investigators will concurrently forward all FDA-reported Serious or unexpected adverse events reports to AZ. A copy of the report must be faxed to AstraZeneca at the time the event is reported to the FDA. All SAEs should be reported to AstraZeneca within 24 hours of the Investigator becoming aware of the event.

* A cover page should accompany the FDA Report form indicating the following:

- **OLAPCO Investigator Sponsored Study** (ISS)
- The investigator **IND number** assigned by the FDA
- **The investigator's name** and **address**
- **The trial name/title** and **AstraZeneca reference number**

* Investigative site must also indicate, either in the SAE report or the cover page, the **causality** of events **in relation to all study medications** and if the SAE is **related to disease progression**, as determined by the principal investigator.

* Send SAE report and accompanying cover page by way of fax (+46 31 776 37 34) or secure email to AstraZeneca using AEmailboxclinicaltrialTCS@astrazeneca.com. Fax is the preferred method. **If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.**

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly. All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events and SAEs will be collected from the time study drug is given, throughout the treatment period and up to and including the *30 day follow-up* period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution.* All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA and AstraZeneca). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

Deaths

All deaths that occur during the study, or within the protocol defined safety follow up period after the administration of the last dose of study treatment, as specified in

section 8.2 above must be reported to AstraZeneca.

8.8.4 Duration of Reporting of SAEs

From the administration of first treatment until 30 days (unless otherwise specified) after the last treatment or withdrawal of subject, new onset adverse events will be captured. Follow-up and reporting of these events will follow the same procedure as for AEs observed during the study period. In addition, any unexpected Serious Adverse Event that occurs more than 30 days after drug administration but is probably/definitely attributed to drug administration .

9 PHARMACEUTICAL INFORMATION

9.1 Pharmaceutical Information

Detailed Pharmaceutical information for each compound is provided in the following appendices:

- Olaparib (B)
- AZD5363 plus olaparib (C)
- AZD6738 plus olaparib (D)
- The AZD1775 plus olaparib arm pharmaceutical information will be added as an addendum to the protocol once the recommended phase II doses are available.

9.2 Pharmaceutical/Drug Distribution

Study drug will be supplied to each study site by AstraZeneca. Participating sites are responsible to ensure processes, procedures, and documentation are in place for storage, distribution, inventory control, and disposition.

9.3 Accountability

The study drug provided for this study is for use only as directed in the study protocol. It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

1. Deliveries of such products from AstraZeneca are correctly received by a responsible person
2. Such deliveries are recorded
3. Study treatments are handled and stored safely and properly as stated on the label
4. Study treatments are only dispensed to study patients in accordance with the protocol

The study personnel will account for all study medications dispensed and returned. Certificates of delivery and return should be signed

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the investigator. This record is in addition to any drug accountability information recorded on the CRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file

10 CORRELATIVE/SPECIAL STUDIES

10.1 Sample collection

10.1.1 Tumor samples

The evaluation of patient eligibility based on mutation data (and FH status by IHC) will be done based on archival / new tumor biopsies prior to enrolment of the study. On the study, the following samples will be collected:

- Archival tumor sample
  - If available, archival tissue will be requested by the enrolling site after consenting procedures are completed. The same sample that was used for the genetic profiling should be requested as a preference, if not available other samples are acceptable
  - Archival tissue should be provided from formalin-fixed and paraffin-embedded tissue. If possible, provide tissue blocks rather than cut sections.
  - Tumor sample collection and storage will be performed as outlined in the laboratory procedure manual
- Tumor sample at baseline if feasible (optional)
  - The sample can be collected up to 4 weeks before the first dose. Therefore, any sample collected during this time period prior to study enrollment can be used as baseline sample
  - The tumor sample for use in genetic and protein analyses (see below) should be formalin-fixed and embedded in paraffin according to standard procedures at each institution
  - Additional tumor samples may also be collected and used fresh or frozen
  - Tumor sample collection and storage will be performed as outlined in the laboratory procedure manual
- Tumor sample at progression or discontinuation if feasible (optional)
  - The sample can be collected at progression or discontinuation, or any time between progression and discontinuation from the study
  - The tumor sample for use in genetic and protein analyses (see below) should be formalin-fixed and embedded in paraffin according to standard procedures at each institution
  - Additional tumor samples may also be collected and used fresh or frozen
  - Tumor sample collection and storage will be performed as outlined in the laboratory procedure manual

10.1.2 Plasma samples

Plasma samples (optional) will be collected at baseline, on treatment and at progression/ discontinuation on study to isolate cell-free circulating tumor DNA (ctDNA) to determine the mutational profile and changes thereof

- The plasma sample (optional) at baseline can be collected up to 2 weeks before the first dose
- Samples on study should be taken at the end of the first cycle (+/- 7 days), and at the end of the cycles 4, 6 and 10 (+/- 7 days) and at progression or discontinuation or any time between progression and discontinuation from the study
- Additional samples after cycle 10 and before progression can be collected (optional), if the investigator deems a particular time point of interest. However, samples should not be collected more frequently than every 2 cycles

- F describes the procedures for collection, processing, storage and shipment of plasma

10.2 Analyses of samples

10.1.1 Analyses of tumor samples

- Genetic analyses of a sample prior to study enrollment is a requirement for enrollment and not part of the study (see B and C for relevant mutations)
- The tumor samples collected at baseline and on progression/ discontinuation, will be used primarily for genetic testing to investigate if the mutational profile of the patients has changed between diagnosis, the start of the study and progression/ discontinuation. Archival samples provided may be used for this purpose too as enrollment is based on multiple accepted CLIA tests.
- Genetic findings will be correlated with outcome and tumor markers, where available.
- Where appropriate, protein- / RNA-analyses will complement the genetic findings on the tumor samples (archival, baseline and progression/ discontinuation samples) to further establish the functional consequence of mutations
- Where possible, patients' cells may also be cultured and retrospectively tested for sensitivity to the relevant agents in exploratory laboratory experiments to study if sensitivity to these agents could potentially be predicted (this will not be done prospectively and not determine enrollment in the study)
- Samples may also be used for additional exploratory endpoints to be defined

While defects in DNA-damage-repair pathways will only be used to select patients for the olaparib monotherapy arm, a focus of the biomarker analyses in the study will be to determine mutations in genes of the DNA-Damage-repair pathway. Mutational analyses of new tumor samples at baseline and on progression, were feasible, is planned, but archival tissue may be used as well.

10.1.2 Analysis of plasma samples

- The plasma samples collected optionally at baseline, on treatment and on progression/ discontinuation, will be used primarily for genetic testing to investigate if the mutational profile of the patient that is detected in tumor samples can also be detected in ctDNA
- Changes in the ctDNA genetic profile as well as quantitative changes in ctDNA levels between the start of the study, on treatment samples and progression/ discontinuation will be evaluated
- Genetic findings will be correlated with outcome and tumor markers, where available.
- Samples may also be used for additional exploratory endpoints to be defined

11 STUDY CALENDAR

Please refer to the following appendices regarding the study calendar for each specific study drug:

- Olaparib (B)
- AZD5363 plus olaparib (C)
- AZD6738 plus olaparib (D)
- The AZD1775 plus olaparib arm study calendar will be added as an addendum to the protocol once the recommended phase II doses are available.

12 MEASUREMENT OF EFFECT

Patients with measurable disease will be assessed by standard criteria. For the purposes of this

study, patients should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained at 4 weeks following initial documentation of a partial or complete response, which ever response is first.

12.1 Antitumor Effect – Solid Tumors

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)[43]. 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.

Evaluable for objective response. Patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re- evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 or patients with therapy stopped due to toxicity prior to completion of one cycle of therapy will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

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 by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with 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. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression by RECIST v1.1 in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 or pathological lymph nodes with ≥ 10 to <15 mm 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.

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. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated. 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.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm 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 or less. If CT scans have slice thickness greater than 5 mm, 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).

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 must have reduction in short axis to <10 mm.

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. (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 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.

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.

Every effort will be made to follow patients to progression/death regardless of future treatment once study treatment is discontinued and they are removed from the study.

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.

12.1.6 Clinical Benefit

Clinical Benefit is defined as the sum of CR, PR, or SD at 16 weeks from the start of treatment.

13 MULTICENTER MANAGEMENT AND COORDINATION

13.1 Data Management

13.1.1 Data Submission

Data will be collected and managed in Yale's web-based clinical trial management system, OnCore. The schedule for completion and submission of the electronic case report forms will be indicated within OnCore.

13.1.2 Data Monitoring

The Yale Center for Clinical Investigation (YCCI) has been designated to monitor this trial. All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13.2 Safety Evaluations

Safety analysis will be conducted on all participants who have received at least one dose of therapy, and will include the frequency of all AEs and laboratory abnormalities as well as frequency of dose interruptions, dose reductions, and treatment discontinuation. Participants who receive one total cycle of treatment will be considered as having completed the evaluation for safety. Additional treatment cycles may be delivered if there are no safety concerns, there is no disease progression, and/or there is an indication of clinical benefit. Maintenance monitoring will occur on day 1 of every additional treatment cycle, unless indicated.

Any safety concern or new information that might affect either the safety or the ethical conduct of this trial will be immediately forwarded to the principal investigator in written form. The principal investigator will be responsible for informing the IRB and Data and Safety Monitoring Committee (DSMC). If trends in toxicities are noted or stopping rules are met, the principal investigator will temporarily suspend enrollment while reviewing the episodes with the IRB and DSMC. Toxicity data must be submitted via OnCore at the end of each cycle of therapy.

13.3 Safety Monitoring

13.1.1 Data and Safety Monitoring Committee

The Yale Cancer Center Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, Adverse Events, Deviations and survival); audit results, and monitoring reports as applicable. Other information (e.g. scans, laboratory values) will be provided upon request.

13.4 Audit Plan

The YCCI Office of Quality Assurance and Training will audit the trial at least annually or as determined by the DSMC. The overall principal investigator, project manager and/or monitor may request access to all source documents and other study documentation for on-site or remote monitoring, audit or inspection.

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator or Yale. The purpose of these audits or inspections is to examine study-related

activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

13.5 Study Site Monitoring

The study principal investigator and YCCI are responsible for monitoring the performance of all of the participating sites. This will be performed by conducting a study site initiation visit, as well as regularly scheduled monitoring visits and/or remote monitoring throughout the life of the protocol. At the end of the trial, the monitor will then perform a study site close-out visit at all participating sites.

YCCI will utilize their institution's initiation, monitoring and close-out visit reports. Following each site visit, a visit report will be generated containing information on site activities, and a summary of pertinent points and action items together with a copy of the follow-up letter will be sent to each investigative site.

During these monitoring visits, some of the items that will be reviewed are the following:

- Training of the sites
- Site personnel qualifications to participate in the trial
- That study related documents are current
- That regulatory compliance is accomplished
- That each subject has signed the informed consent
- That the current and approved protocol is complied with (including reporting and logging of all protocol deviations)
- That all SAEs and AEs have been reported to the local regulatory and Ethics/IRB Committees, YCCI and Astra Zeneca, as appropriate
- That source documentation matches CRFs
- That required procedures for study drug accountability, distribution, and storage are followed.

YCCI will document the required study monitoring activities in a Study Monitoring Plan.

13.6 Protocol Research Team Meetings

Scheduled meetings will be held via teleconference monthly, or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and research staff involved with the conduct of the protocol.

During these meetings the investigators will discuss:

- Safety of protocol participants (adverse events and reporting)
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrollment rate relative to expectation of target accrual, (eligible and ineligible\participants)
- Retention of participants, adherence to the protocol and protocol violations
- Protocol amendments

13.7 Tissue Donor Privacy and Confidentiality

We recognize that the process of both contribution and access to human specimens needs to be transparent and governed by sound ethical and scientific principles so we can assure our patients that their free donations are put to as appropriate a use as possible. We feel confident that the

studies performed with these specimens are important, are covered by the individuals' initial consent, and pose no greater than minimal risk.

It is the responsibility of the coordinating site-Principal Investigator to ensure that confidentiality for all patients participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted must never contain the name of a trial participant. Each patient in the trial will be identified by a unique identifier that will be used on all CRF's and any other material. All case report forms and any identifying information will be kept in a secure location with access limited to the study staff directly participating in the trial.

Personal medical information may be reviewed by representatives of the coordinating site (Yale), of the IRB or of regulatory authorities in the course of monitoring the progress of the trial. Every reasonable effort will be made to maintain such information as confidential. Personal identifying information will only be released with the express written permission of the tissue/blood donor along with IRB approval.

The results of the study may be presented in reports, published in scientific journals or presented at medical meetings; however, patient names will never be used in any reports about the study.

13.7.1 Access to Biospecimens and Donor Information

Only personnel authorized by the Principal Investigators will have direct access to the specimen storage facilities and samples, including records pertaining to the identity of participants. Authorized study personnel at Yale will keep a copy of the signed consent form and the key linking the unique identifiers to the patient PHI. The master list linking the patient PHI and unique study identifiers will be kept in the Yale OnCore computer system with electronic safeguards. The access is limited to the designated Yale study personnel. Other than elements of dates that will possibly be needed by the Clinical Tumor Board to identify potential appropriate treatments (i.e. dates of initial diagnosis or prior treatment dates), and the unique de-identified coded sample number, no PHI will be shared with entities outside of Yale.

Standard Yale procedure is to train requested staff on OnCore's Biospecimen Module (BSM) role and assign that to them. The scope of the role is limited to the protocol, in this case the Phase I program at Yale. Therefore, the assigned Data Manager with this role would be able to access the BSM Console for entry and management of specimens on the protocol.

13.7.2 Biospecimen Banking

Specimens will be collected and stored as per the laboratory procedure manual.

13.7.3 Future Use of Banked Samples:

Patients will have the option during the consent process of allowing their specimens to be used for additional medical research beyond the scope of this study, provided the specimens are completely de-identified. Use of this material will require prior review and approval by the IRB or record at the recipient investigator's site and approval from study Principal Investigators. Other than the de-identified sample number, no PHI will remain with the biobank-stored specimen.

13.7.4 Restrictions on Sample Usage

The intended use for these samples is to facilitate research. All investigators receiving samples will be reminded of their ethical and regulatory responsibilities concerning the use of such samples by providing them the following statement:

The recipient of any human samples will acknowledge that the conditions for use of this research material are governed by their site IRB in accordance with Department of Health and Human Services regulations noted in 45 CFR 46. The recipient agrees to comply fully with all such conditions and to report promptly to their IRB any proposed changes in the research project and any unanticipated problems involving risks to subjects or others. The recipient remains subject to applicable State or local laws or regulations and institutional policies that provide additional protections for human subjects. This research material may only be used in accordance with the conditions stipulated by the IRB.

13.7.5 Incidental Findings

During the course of data analysis, investigators may discover genetic information about the study participant that is not related to the current study (an incidental finding). We will follow the guidelines outlined by the American College of Medical Genetics and Genomics (ACMG) for incidental variants of known significance, when encountered (45). Investigators will consult with a genetic counselor if needed.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

14.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to AstraZeneca and/or allow AstraZeneca, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

14.3 Informed consent

Provision of written Informed Consent must be obtained prior to any study-related procedures. The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be stored. A copy of the signed written Informed Consent Form must be given to the subject.

15 STATISTICAL CONSIDERATIONS

15.1 Sample Size Justification and Decision Rules

The sample size estimation for each single arm of this phase II study is based on the objective response rate (ORR). A two-stage "minimax" accrual design described by Simon will minimize the maximum number of patients exposed to treatment for a set of assumed values of the design parameters [44]. These parameters are: (i) probability of response ≤ p_0, where p_0 defines the ineffective treatment response proportion, (ii) probability of response ≥ p_1, where p_1 defines the effective treatment response proportion, (iii) *power* = 1 - probability of Type II error, and (iv) α = probability of Type I error. For this study, the assumed design parameters are p_0 = 0.10, p_1 = 0.30, *power* = 0.90, α = 0.10. If there is evidence, at the conclusion of stage 1 or stage 2, that the true underlying ORR is at least 30% for a treatment arm, consideration will be given for further testing of that treatment. However, if the results at the conclusion of stage 1 provide evidence that the treatment is inactive in patients, i.e. ORR less than 10%, then the treatment arm will be terminated early.

From the design parameters given above we derive the two-stage sample sizes and decision rules. Stage 1: Initially, 16 patients per arm will be enrolled into the study and treated at stage 1. If there are less than 2 responses among these first 16 subjects, accrual to the treatment arm will be terminated based on evidence that it is likely that ORR ≤ 10% and unlikely that ORR ≥ 30%. If there are at least 5 responses among the first 16 patients, recruitment to 25 patients will continue in the treatment arm, but further development may be considered. If there are at least two but less than 5 responses in these first 16 patients, the trial will continue to stage 2 for the treatment arm until 25 patients have been treated. If there are at least 5 responses in these 25 patients, then further development of the treatment will be considered.

Some additional operating characteristics for this design are: expected number (i.e. frequentist mean number) of patients exposed when true ORR is 10% = 20.4; expected number of patients exposed when true ORR is 30% = 24.8; the probability of early termination for futility when true ORR is 10% = 0.515; the probability of early termination for futility when true ORR is 30% = 0.026.

This design provides 90% statistical power to detect a difference of 20% (successful treatment = 30% vs. futile treatment = 10%) with a type I error probability less than 0.10.

15.2 Early Stopping Rule for Safety

We will monitor the study for safety in the first 16 patients in each single arm. If we observe 4 or more patients with unacceptable toxicity in the first 16 patients, then the arm will be terminated early. Unacceptable toxicity is defined for this protocol as CTCAE Grade 4 hematological and CTCAE Grade 3 non-hematological toxicities that fail to resolve to Grade 1 despite appropriate supportive care. With this design, the probability of terminating any arm early is 0.07 if the true but unknown unacceptable toxicity rate is 10%, and 0.75 if the true toxicity rate is 30%.

15.3 Statistical Analysis

15.3.1 Analysis Sets

Full Analysis Set: all enrolled patients.

Safety Analysis Set: all patients who receive at least one treatment dose.

Efficacy Analysis Set: all patients who receive at least one treatment dose and are evaluable for post-baseline response status.

15.3.2 General Methods

Analyses will be performed separately for each treatment arm, as if they are four parallel studies within one protocol.

Descriptive statistics, including means, standard deviations, medians and ranges for continuous scale parameters, as well as percent and frequencies for categorical parameters, will be presented. For time-to-event parameters, estimates of median survival with 95% confidence intervals will be calculated, and Kaplan Meier plots will be provided. 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.

No corrections for multiplicity will be performed.

15.3.3 Disposition, Demographics, and Baseline Clinical Characteristics (Full Analysis Set)

Patient disposition will be listed and tabulated by treatment arm. Demographic information including but not limited to age, gender and race, will be tabulated by treatment arm. Other baseline characteristics, such as medical history, concomitant medications, disease severity, time from diagnosis, physical exam and lab test results will be presented similarly.

15.3.4 Safety and Toxicity (Safety Analysis Set)

Adverse events (AEs) will be listed and tabulated by treatment arm. AEs will be classified based on the likelihood that they are treatment-related. NCI toxicity Grade 3 and Grade 4 laboratory abnormalities will also be listed. PFS analysis will also be performed with patients in the safety analysis set.

15.3.5 Efficacy (Efficacy Analysis Set)

The efficacy of each treatment will be assessed by analysis of the primary endpoint using the 16 week response status. The exact Binomial method will be used to calculate two-sided 95% confidence intervals for ORR. Multivariate logistic regression will be used to predict the ORR by including patient characteristics variables and other clinically relevant factors as covariates.

For time-to-event endpoints, Kaplan-Meier plots and estimates for median survival time with 95% confidence intervals will be provided for each treatment arm.

15.3.6 Subgroup Analyses

Due to the limitation of the sample size, we will not have sufficient power to perform official statistical tests to detect differences between patients with different tumor types or mutations. Descriptive statistics will be used to present ORR by tumor type and by specific mutation. Data permitting, survival function of patients in subgroups will also be summarized.

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: Olaparib in Patients with HDR Gene Mutations & IDH1/IDH2 Mutations

Treatment of patients with solid tumors that harbor DNA damage repair gene mutations or neomorphic oncometabolites, such as 2-HG, in patients harboring mutations in IDH1/IDH2 mutant tumors or TCA/tricarboxylic acid cycle mutations such as FH and/or SDH is part of the clinical trial outlined in the main protocol.

Defects in components of the HDR/DSB repair mechanism require affected cells to depend on alternative error-prone pathways of DNA repair, including BER and B-NHEJ. PARP1 hyperactivity has been demonstrated in HDR-defective cells and ought to confer a similar sensitivity to PARP inhibitors, which target the essential DDR pathway remaining intact in HDR deficient cells [45]. This has led to the concept of "*BRCA-ness*", which proposes that somatic mutations in the BRCA 1 and 2 genes, as well as other HDR genes as noted above, should confer a similar sensitivity to PARP inhibitors as gBRCA mutations. This expanded repertoire of mutations in HDR should be considered as potential clinical targets for DDR-focused therapies such as PARP inhibitors. This would include somatic mutations of BRCA 1 & 2, the BRCA interacting proteins of the MRN complex (MRE11, RAD 50, NBS), RAD51, PALB2/FANCN, FANCD2, FANCC and DSS1. This grouping of BRCA-interacting proteins can be considered the HDR effector arm or RAD51 foci-forming proteins. Another grouping of DDR proteins includes the checkpoint controllers ATM, ATR, CHK1 and CHK2, which regulate cell cycle and the expression of the HR effector proteins such as BRCA1. Other DDR proteins comprise the FANCA/B/C/E/F/G/L/M complex core, which activates FANCD2, thus localizing the HDR repair effector complex to the site of DSB and SSB, plays a critical role in DDR such that loss of any of the components has a profound repair-defective phenotype.

In fifty consecutive 50 tumors profiled at Yale, nonsense mutations and mutations considered to have major effects on DNA damage repair pathways at critical functional sites (COSMIC) were detected in 8 (16%). This incidence makes identifying appropriate patients for this study feasible. These aberrations were detected in multiple different tumor types including GBM, H&N cancer, NSCLC, prostate, breast, colorectal and other solid and hematological malignancies.

This appendix contains details and study requirements that are specific to treatment with olaparib, including:

AB-1 MATERIALS AND METHODS

AB-1.1 PATIENTS

Eligible patients must meet all of the eligibility requirements contained in the main study protocol.

AB-1.1.1 Inclusion Criteria

Refer to the main protocol Inclusion Criteria.

AB-1.1.2 Additional Exclusion Criteria

Refer to the main protocol Exclusion Criteria.

AB-1.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (STUDY DESIGN AND RATIONALE).

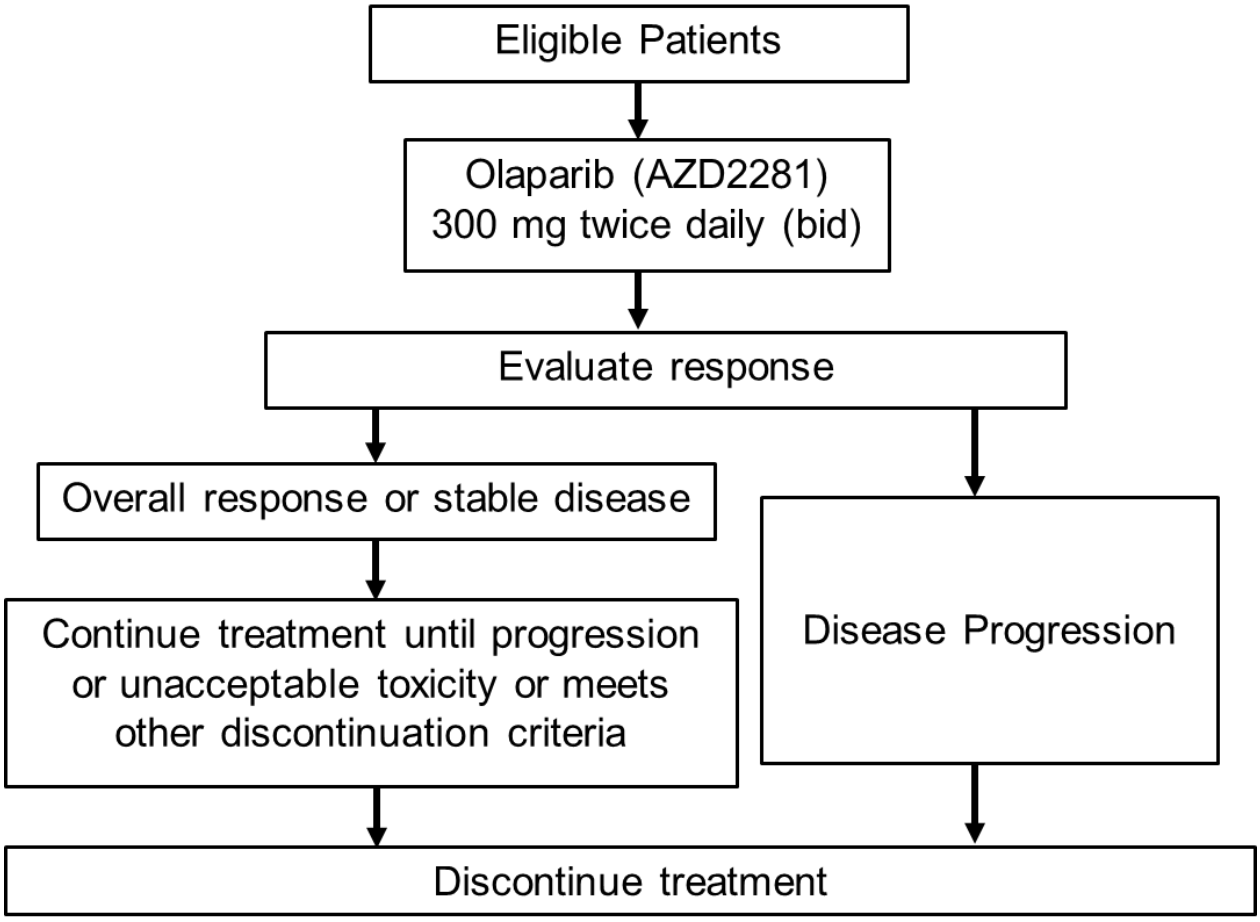
AB-1.3 STUDY TREATMENT

All patients will receive treatment with olaparib, given at a bid daily dose of 300 mg orally (PO) in cycles of 28 days (4 weeks) duration. A schema of the study design is presented in Study Schema: Olaparib.

All patients will receive:

- Olaparib 300 mg bid daily tablets.
- No routine premedications are required.

AB-Figure 1: Study Schema: Olaparib



AB-1.3.1 Olaparib

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB)

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerization (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 (Tumors with HDR deficiencies, such as serous ovarian cancers, 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.

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. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

PARP inhibitors such as olaparib may also enhance the DNA damaging effects of chemotherapy.

For further information, please refer to the current version of the olaparib IB.

a. Formulation

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

Laboratory Codes: AZD2281; KU-0059436; CO-CE 42

CAS No.: 763113-22-0

Molecular Formula: C24H23FN4O3

Molecular Weight: 434.46

b. Dosage, Administration, and Storage

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the investigator as round or oval *green film coated tablets*

AC-Table 1: Olaparib dosage form and strength

Investigational product	Dosage form and strength
Olaparib	*100 mg tablet*
Olaparib	*150 mg tablet*

Descriptive information for olaparib can be found in the Investigator's Brochure

For all centers, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 32 tablets and desiccant. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Olaparib will be dispensed to patients on Day 1 of each cycle until the patient completes the study, withdraws from the study or closure of the study.

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose (e.g. forgetting to take the tablets or vomiting) or need to modify the timing of a scheduled dose for any reason, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours before or after that scheduled dose time. The dose should not be taken more than 2 hours in advance of the scheduled dose time. If greater than 2 hours has passed 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. Doses should not be taken fewer than 10 hours apart.

Food intake restrictions

Olaparaib doses can be taken without regard to food. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided

Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The product should be stored in the pack provided and used according to the instructions on the label.

Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrolment code (E-code) to be completed at the time of dispensing.

The label will include the following information:

- blank lines for quantity of tablets to be taken
- enrolment code (E-code)
- date of dispensing
- Instructions stating that the olaparib tablets should be taken at approximately the same time each morning and evening

c. Dosage Modification

Toxicities will be evaluated utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

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

Olaparib has been tested in a standard range of safety pharmacology studies e.g. dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioral, autonomic or motor effects in the rat at the doses studied.

The toxicology studies indicate that the target organ of toxicity is the bone marrow.

Further information can be found in the current version of the olaparib Investigator's Brochure

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

The administration of olaparib may be delayed to assess or treat adverse events (AEs). Once a dose level reduction has occurred, the dose level may not be re-escalated.

Any toxicity observed during the study could be managed by interruption and/ or dose reduction of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. Olaparib must be interrupted until the patientrecovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (current version) grade 1 or less. If a dose is interrupted, drug should be resumed beginning the next cycle according to the schedule of assessments.

Where toxicity reoccurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue treatment with olaparib.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib.

Dose Modifications Due to Hematologic Toxicity

Dose modifications on Day 1 of each cycle will be based on blood counts determined on the day of scheduled treatment. Nadir blood counts will not be used to determine dose modifications. Treatment on Day 1 of any cycle will proceed if blood counts demonstrate absolute neutrophil count (ANC) ≥ 1500/μL, hemoglobin (Hgb) ≥ 10 g/dL, and platelets ≥ 100,000/μL.

AB-Table 2: Dose Modifications for Hematologic Toxicity

Day 1 Blood Counts	Olaparib
ANC ≥1500/ul; Hgb ≥10 g/dl; Platelets ≥100,000/ul	**No dose modification**
ANC ≤ 1500/ul or Hgb ≤10 g/dl or Platelets ≤ 100,000/ul 1st incidence	**Hold until count recovery, then restart without dose modification**
ANC ≤ 1500/ul or Hgb ≤10 g/dl or Platelets ≤ 100,000/ul 2nd incidence	**Reduce to 250 mg bid**
ANC ≤ 1500/ul or Hgb ≤10 g/dl or Platelets ≤ 100,000/ul 3rd incidence	**Reduce to 200 mg bid**
ANC ≤ 1500/ul or Hgb ≤10 g/dl or Platelets ≤ 100,000/ul 4th incidence	**Discontinue**

ANC = absolute neutrophil count; PO = orally.

Note: olaparib should be discontinued if hematologic toxicity does not resolve (ANC ≥ 1500/μL, Hgb ≥ 10 g/dL, and platelets ≥ 100,000/μL) within 28 days.

Management of anemia
Adverse events of anemia CTCAE grade 1 or 2 (Hemoglobin (Hgb) ≥ 8 g/dl) should be investigated and managed as deemed appropriate by the investigator (This can include ESA/erythropoietin stimulating agents or PRBCs/packed red blood cell transfusions) with or without interruption of study drug or change in dose, in accordance with the table above and considering previous history of anemia. Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases, management of anemia may require blood transfusions. However, if a patient develops anemia CTCAE grade 3 (Hgb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the patient should be managed appropriately. Study treatment can be restarted at the same dose if Hgb has recovered to ≥ 10 g/dl. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

If a patient has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by investigator, study treatment should be permanently discontinued.

Management of neutropenia and leukopenia
Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leukopenia have been recovered up to CTC AE grade ≥1 (ANC ≥ 1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step for a 300 mg monotherapy starting dose.

Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If a patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. In some cases, management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥ 2-week interruption/delay in study treatment due to CTC 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 (calculate reticulocyte index (RI), RI = reticulocyte count x hematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to 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 an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

The dose of olaparib **must not** be adjusted under any other circumstances unless the AstraZeneca Study Physician gives prior agreement.

Dose Modifications Due to Non-Hematologic Toxicity

AB-Table 3: Dose Modifications for Non-Hematologic Toxicity

CTCAE Grade	Action	Olaparib dose reduction
Grade 1-2 (tolerable)	Maintain Dose	No dose modification
Grade 2 (intolerable) or Grade 3		
1st Appearance	Hold until recovery ≤ Grade 1, then resume with recommended dose modifications	200 mg bid
2nd Appearance	Hold until recovery ≤ Grade 1, then resume with recommended dose modifications	Discontinue treatment
Grade 4		
1st Appearance	Hold until recovery ≤ Grade 1, then resume with recommended dose modifications	200 mg bid
2nd Appearance	Discontinue treatment	Discontinue treatment

CTCAE = Common Terminology Criteria for Adverse Events. Bid = twice daily.

If Grade 3 or 4 non-hematologic toxicity (other than nausea, vomiting) occurs, treatment with olaparib should be held. Treatment with olaparib should be resumed according to Dose Modifications for Non-Hematologic Toxicity as soon as the toxicity resolves to ≤ grade 1.

Management of new or worsening pulmonary symptoms
If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

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

Management of nausea and vomiting
Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No stoppage of olaparib is required for any biopsy procedures.

Olaparib should be discontinued for a minimum of 7 days before a patient undergoes therapeutic palliative radiation treatment.

Other Toxicities

Olaparib dosing should be discontinued for any severe toxicity that does not respond to treatment.

d. Olaparib Warnings and Precautions

MDS/AML

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 gBRCA 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

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 events have been reported in <1% of patients receiving olaparib. The 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 an abnormal 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.

Pregnancy

Pre-clinical data indicate that olaparib can have adverse effects on embryo-fetal survival and development and pregnancy is an Exclusion Criterion for the clinical studies with Olaparib. If any patient becomes pregnant during a study, olaparib must be discontinued and the patient followed up until birth or termination of pregnancy. The clinical protocol gives details on the requirements to report pregnancy and its outcome. Should pregnancy occur, the physician and patient should discuss the risks of continuing the pregnancy.

Male patients should refrain from fathering a child or donating sperm during a study and for 6 months following the last dose of Olaparib.

Contraception

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 and for 6 months after last dose of study drug(s).

Condom with spermicide and one of the following:

- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- 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 (e.g., Implanon, Norplan)+male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Hormonal shot or injection (eg, Depo-Provera) + male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system -Mirena®) + male condom
- Norelgestromin/ethinyl estradiol (EE) transdermal system + male condom with spermicide
- Intravaginal device + male condom with spermicide (e.g., EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

Lactation
Lactation is an Exclusion Criterion within the study protocols for olaparib. It is not known whether olaparib is excreted in human milk.

Pregnancy
All outcomes of pregnancy should be reported to AstraZeneca.

Maternal exposure
If a patient becomes pregnant during the study olaparib should be discontinued immediately.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day** i.e., immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

Paternal exposure
Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

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 bid (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs during the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply. For other overdoses, reporting should be done within 30 days.

e. **Metabolism and Drug Interactions**
The use of any natural/herbal products or other "folk 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 eCRF.

Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following strong inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known strong inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, idinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

For patients taking any of the above, the required wash-out period prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following strong CYP3A4 inducers should be avoided:

- Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitol, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting olaparib are:

- phenobarbitol 5 weeks, and for any of the others, 3 weeks.

After randomization, if the use of any strong inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Other Concomitant Medications

Any medications, other than those listed as excluded therapies, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

Anticoagulant Therapy: Patients who are 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. Subcutaneous heparin is permitted.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF.

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

For further detail, see the Investigator's Brochure (IB).

AB-1.4 CONCOMITANT AND EXCLUDED THERAPIES

AB-1.4.1 Concomitant Therapy

Refer to the main body of the protocol (Concomitant and Excluded Therapies) for concomitant therapies allowed.

Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Full details of these treatments must be recorded in the patient's

notes and appropriate section of the eCRF. Study treatment should be discontinued for a minimum of 3 days before the patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks if bone marrow toxicity has resolved.

AB-1.4.2 Excluded Therapy

The following restrictions apply during the entire duration of study treatment:

- No other investigational therapy should be given to patients.
- No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial. The patient can receive a stable dose of corticosteroids during the study if these were started at least 4 weeks prior to treatment, as per exclusion criteria. Bisphosphonates and Denosumab for bone metastases are allowed if these were started at least 4 weeks prior to treatment with study drug. Octreotide is allowed if dose is stable for >3 months with no worsening of carcinoid syndrome. Hormonal therapy with luteinizing hormone-releasing hormone (LHRH) analogues for medical castration in patients with castrate-resistant prostate cancer are permitted. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics if no evidence of disease progression is present.
- Live virus and bacterial vaccines should not be administered whilst 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 are unknown.
- Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days after the last dose of study medication. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, this restriction is required to ensure patient safety.

AB-1.5 STUDY ASSESSMENTS

	Screening	Day 1 of Cycle 1	Day 1 of each cycle[j]	Every 8 weeks	End of Study	30 Day Follow-up	Long term Follow Up as per main protocol
Visit window (days)	28[i]	+/- 3	+/- 3	+/- 3	+/- 3	+/- 7	+/- 7
Informed consent	X						
Inclusion/Exclusion Criteria	X						
Pregnancy Test[a]	X	X					
Molecular Selection of Patients based on Archival Tumor Tissue (Paraffin embedded)	X						
Medical History	X						
Physical examination, weight and vital signs [b]	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Laboratory tests (Clinical Chemistry/hematology/urinalysis/coagulation)[c]	X	X[h]	X		X[d]		
Concomitant medications	X	X	X		X		
Dosing compliance		X	X		X		
Adverse events	X	X	X	X	X	X	
RECIST Assessments [e]	X			X	X	X	
Tumor Tissue (Paraffin embedded) (optional)[f]		X			X		
Plasma Sample[g]		X		X	X		
Anti-cancer therapy follow-up							X

a Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. 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.

b A complete physical examination will be performed at the following timepoints (within 24 hours of visit): 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). Vital signs (heart rate, systolic and diastolic blood pressure, oxygen saturation (pulse oximetry), respiration rate, weight, height (at screening) and temperature)

c 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 thromboplastin 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. If APTT testing is not locally available, Partial Thromboplastin Time (PTT) testing may be done along with INR. Any clinically significant results on PTT will be confirmed with APTT.

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 AstraZeneca Patient Safety for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

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]).

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.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities.

These tests will be performed by the hospital's local laboratory. There is a 48 hr window for performance of lab testing for each visit. 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 G 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

d 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.

e 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. 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).

f Tumor sample at baseline if feasible (optional). The sample can be collected up to 4 weeks before the first dose. Therefore, any sample collected during this time period prior to study enrollment can be used as baseline sample. The tumor sample for use in genetic and protein analyses should be formalin-fixed and embedded in paraffin according to standard procedures at each institution. Additional tumor samples may also be collected and used fresh or frozen.

Tumor sample at progression or discontinuation if feasible (optional). The sample can be collected at progression or discontinuation, or any time between progression and discontinuation from the study. The tumor sample for use in genetic and protein analyses should be formalin-fixed and embedded in paraffin according to standard procedures at each institution. Additional tumor samples may also be collected and used fresh or frozen

g Plasma samples (optional) will be collected at baseline, on treatment and at progression/ discontinuation on study to isolate ctDNA to determine the mutational profile and changes thereof. The plasma sample at baseline can be collected up to 2 weeks before the first dose. Samples on study should be taken at the end of the first cycle (+/- 7 days), and at the end of the cycles 4, 6 and 10 (+/- 7 days) and at progression or discontinuation or any time between progression and discontinuation from the study

Additional samples (optional) after cycle 10 and before progression can be collected, if the investigator deems a particular time point of interest. However, samples should not be collected more frequent than every 2 cycles. F describes the procedures for collection, processing, storage and shipment of plasma

h. Results of all cycle 1 day 1 laboratory tests must re-meet eligibility criteria
i: Screening to be performed within 28 days unless otherwise specified
j: Continuous use of Olaparib is suitable during this window

APPENDIX C: AZD5363 plus olaparib in patients with AKT, PIK3CA, or ARID1A mutations or other aberrations leading to dysregulation of the PI3K/AKT pathway

Treatment of patients with solid tumors that harbor *PTEN, PIK3CA*, *AKT,* or *ARID1A* mutations or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway is part of the clinical trial outlined in the main protocol.

AZD5363 is an inhibitor of AKT1, AKT2 and AKT3. Patients with tumors harboring *PTEN, PIK3CA*, *AKT,* or *ARID1A* mutations or other molecular aberrations leading to dysregulation of the PI3K/AKT pathway are considered most likely to be sensitive to AKT inhibition and will be treated with AZD5363 plus olaparib.

Increased AKT phosphorylation has been shown to occur in tumors with ARID1A deficiency and these tumors have been shown to be sensitive to treatment with the AKT inhibitor MK-2206 [37-39] Patients with ARID1A mutations can therefore be included in the AZD5363 plus olaparib combination arm.

Preclinical data suggest that *PIK3CA* mutations predict response to PI3K-, AKT-, or mTOR inhibitors, including AZD5363, whereas mutations in RAS genes predict resistance [46]. *PIK3CA* mutations have been detected in up to 10% of advanced tumors. Tumor types with high frequencies include breast cancer (>20%), endometrial cancer ((>20%), urinary tract cancers (>20%), cervical cancer (>10%), melanoma (>10%), colorectal cancer (>10%), ovarian cancer, gastric cancer, biliary tract tumors, and esophageal cancer, non-small cell lung cancer [NSCLC], and squamous cell head and neck cancer [47-51] (http://www.sanger.ac.uk/genetics/CGP/cosmic/). A retrospective analysis of patients that were treated with different PI3K- or AKT- or mTOR inhibitors in multiple studies, *PIK3CA* or *PTEN* mutations were predictive of response, suggesting that tumors harboring *PIK3CA* or *PTEN* mutations are more sensitive to inhibition of this pathway by PI3K-, AKT-, or mTOR-inhibitors [47].

PIK3R1 and *PIK3R2*, which encode regulatory subunits of PI3K, have been identified in in >20% and 5% of endometrial cancers with lower frequencies in other cancers. In addition to loss of function of the PI3K regulatory subunit, gain of function mutations were identified, that destabilize PTEN [48, 52]. TCGA studies identified *PIK3R1* mutations also in colorectal, gastric and bladder cancer, glioblastomas and other cancers (cBioPortal for Cancer Genomics, 2013).

AKT1 mutations are found at low frequency in a number of tumor types. The most common mutation is E17K, which has been shown to be transforming and increases localization to the membrane where AKT is activated [53]. In a panel of tumor samples the occurrence of *AKT1E17K* mutation was detected in 5.9%, 1.1% and 0.6% of breast, colorectal and lung cancers, respectively [54]. *AKT1E17K* mutations have been characterized in 1–8% of breast carcinomas, both ductal and lobular histotypes and are mutually exclusive with respect to the *PIK3CA E545K* or *H1047R* alleles [53]. *AKT1E17K* mutations have also been detected in endometrial carcinomas, mainly limited to high grade, advanced stage tumors suggesting a link of this mutation with a more aggressive cancer disease, as well as in low frequency in NSCLC and SCC [55-60]. Shoji et al found that *AKT1E17K* mutant tumors do not harbor coexisting mutations in *PTEN, PIK3CA or KRAS* [56]. AKT1 mutations have also been found in meningeal, urinary tract, prostate, skin and other cancers [48].

Rare mutations in *AKT2* and *AKT3* have also been found in various cancers, although it is not known whether some of these are transforming. For example, *AKT2* mutations were found in 1/51 gastric and 2/79 lung cancers, and in an independent study, in 2/43 non-small cell lung cancers (NSCLCs) [61, 62]. Mutations in *AKT3* have been reported in melanoma at 1.5% frequency [63]. In endometrial cancer, rare mutations in *AKT2* and *AKT3* have been reported [64].

This appendix contains details and study requirements that are specific to treatment with AZD5363 plus olaparib, including:

AC-1 MATERIALS AND METHODS

AC-1.1 PATIENTS

Eligible patients must meet all eligibility requirements contained in the main study protocol. Listed here are additional requirements specific to treatment with the combination of AZD5363 and olaparib.

AC-1.1.1 Additional Inclusion Criteria Refer to the main protocol Inclusion Criteria.

AC-1.1.2 Additional Exclusion Criteria Refer to the main protocol Exclusion Criteria.

AC-1.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (STUDY DESIGN AND RATIONALE).

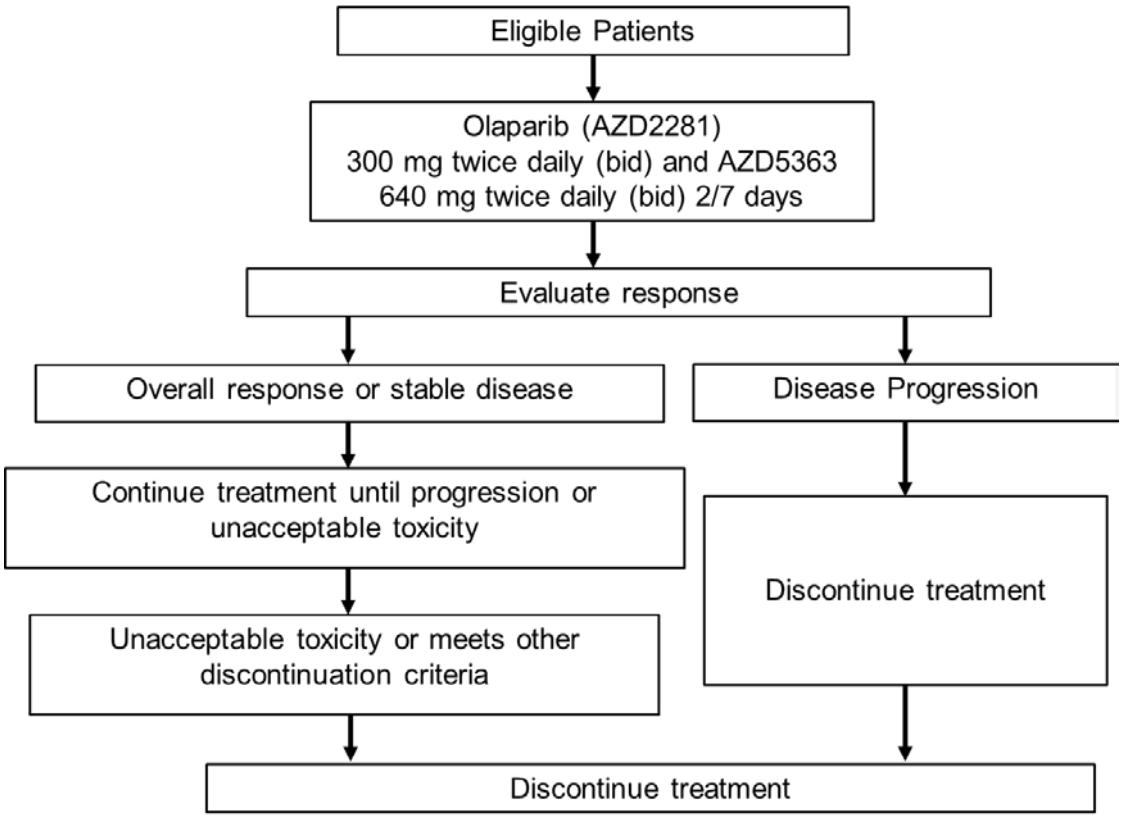
AC-1.3 STUDY TREATMENT

All patients will receive treatment with AZD5363, given at a dose of 640 mg bid for 2 days on 5 days off (2/7) in cycles of 28 days (4 weeks) duration. A schema of the study design is presented in Study Schema: AZD5363 and olaparib.

All patients will receive:

- Olaparib 300 mg bid and AZD5363 at a dose of 640 mg bid.
- No routine premedications are required.

AC-Figure 1: Study Schema: AZD5363 and olaparib



AC-1.3.1 Olaparib

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB)

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose] (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). polymerization Tumors with HDR deficiencies, such as serous ovarian cancers, 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.

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. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

PARP inhibitors such as olaparib may also enhance the DNA damaging effects of chemotherapy.

For further information, please refer to the current version of the olaparib IB.

a. Formulation

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

Laboratory Codes: AZD2281; KU-0059436; CO-CE 42

CAS No.: 763113-22-0

Molecular Formula: C24H23FN4O3

Molecular Weight: 434.46

b. Dosage, Administration, and Storage

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the investigator as round or oval *green film coated tablets*

AD-Table 1: Olaparib dosage form and strength

Investigational product	Dosage form and strength
Olaparib	*100 mg tablet*
Olaparib	*150 mg tablet*

Descriptive information for olaparib can be found in the Investigator's Brochure

For all centers, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 32 tablets and desiccant. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Olaparib will be dispensed to patients on Day 1 of each cycle until the patient completes the study, withdraws from the study or closure of the study.

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

If vomiting occurs shortly after the olaparib 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 (e.g. forgetting to take the tablets or vomiting) or need to modify the timing of a scheduled dose for any reason, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours before or after that scheduled dose time. The dose should not be taken more than 2 hours in advance of the scheduled dose time. If greater than 2 hours has passed 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. Doses should not be taken fewer than 10 hours apart.

Combination drug should be given at least 1 hour after the patient has taken their olaparib morning dose.

Food intake restrictions

Olaparib doses can be taken without regard to food. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided

Storage
All study drugs should be kept in a secure place under appropriate storage conditions. The product should be stored in the pack provided and used according to the instructions on the label.

Labelling
Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrolment code (E-code) to be completed at the time of dispensing.

The label will include the following information:

- blank lines for quantity of tablets to be taken
- enrolment code (E-code)
- date of dispensing
- Instructions stating that the olaparib tablets should be taken at approximately the same time each morning and evening

c. Dosage Modification

Toxicities will be evaluated utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

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

Olaparib has been tested in a standard range of safety pharmacology studies e.g. dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioral, autonomic or motor effects in the rat at the doses studied.

The toxicology studies indicate that the target organ of toxicity is the bone marrow.

Further information can be found in the current version of the olaparib Investigator's Brochure

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

The administration of olaparib may be delayed to assess or treat adverse events (AEs). Once a dose level reduction has occurred, the dose level may not be re-escalated.

Any toxicity observed during the study could be managed by interruption and/ or dose reduction of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as

required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (current version) grade 1 or less. If a dose is interrupted, drug should be resumed beginning the next cycle according to the schedule of assessments.

Where toxicity reoccurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue treatment with olaparib.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib.

Dose Modifications Due to Hematologic Toxicity
Dose modifications on Day 1 of each cycle will be based on blood counts determined on the day of scheduled treatment. Nadir blood counts will not be used to determine dose modifications. Treatment on Day 1 of any cycle will proceed if blood counts demonstrate absolute neutrophil count (ANC) ≥ 1500/μL, hemoglobin (Hgb) ≥ 10 g/dL, and platelets ≥ 100,000/μL.

Please see Dose Modifications for Hematologic Toxicity for dose modifications due to hematologic toxicity.

Management of anemia
Adverse events of anemia CTCAE grade 1 or 2 (Hemoglobin (Hgb) $\geq$ 8 g/dl) should be investigated and managed as deemed appropriate by the investigator (including ESA/erythropoietin stimulating agents and PRBC/packed red blood cells) with or without interruption of study drug or change in dose, in accordance with the Table AB-2 and considering previous history of anemia. Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases, management of anemia may require blood transfusions. However, if a patient develops anemia CTCAE grade 3 (Hgb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the patient should be managed appropriately. Study treatment can be restarted with dose reductions as outlined in Dose Modifications for Hematologic Toxicity.

If a patient has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by investigator, study treatment should be permanently discontinued.

Management of neutropenia and leukopenia
Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.

Study treatment can be restarted as per Dose Modifications for Hematologic Toxicity if an adverse event of neutropenia or leukopenia have been recovered up to CTC AE grade $\geq$1 (ANC $\geq$ 1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require study treatment dose reductions found in Dose

Modifications for Hematologic Toxicity.

Management of thrombocytopenia
An adverse event of thrombocytopenia should be managed as deemed in Dose Modifications for Hematologic Toxicity. If a patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. Management of thrombocytopenia may require platelet transfusions. Platelet transfusions.

Management of prolonged hematological toxicities while on study treatment
If a patient develops prolonged hematological toxicity such as:

- ≥ 2 week interruption/delay in study treatment due to CTC 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 (calculate reticulocyte index (RI), RI = reticulocyte count x hematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to 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 an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

The dose of olaparib **must not** be adjusted under any other circumstances unless the AstraZeneca Study Physician gives prior agreement.

Dose Modifications Due to **Non-Hematologic Toxicity**

Management of new or worsening pulmonary symptoms
If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.
All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Management of nausea and vomiting
Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however,

patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines

Additional information for patients
Olaparib should be stopped before surgery and re-started after wound has healed following recovery.

No stoppage of olaparib is required for any biopsy procedures.

Olaparib should be discontinued for a minimum of 7 days before a patient undergoes therapeutic palliative radiation treatment.

Other Toxicities
Olaparib dosing should be discontinued for any severe toxicity that does not respond to treatment.

Please refer to Dose Modifications for Non-Hematologic Toxicity for dose modifications due to non-hematologic toxicities.

d. Olaparib Warnings and precautions

MDS/AML
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 gBRCA 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

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 events have been reported in <1% of patients receiving olaparib. The 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 an abnormal 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.

Pregnancy

Pre-clinical data indicate that olaparib can have adverse effects on embryo-fetal survival and development and pregnancy is an Exclusion Criterion for the clinical studies with Olaparib. If any patient becomes pregnant during a study, olaparib must be discontinued and the patient followed up until birth or termination of pregnancy. The clinical protocol gives details on the requirements to report pregnancy and its outcome. Should pregnancy occur, the physician and patient should discuss the risks of continuing the pregnancy.

Male patients should refrain from fathering a child or donating sperm during a study and for 6 months following the last dose of Olaparib.

Contraception

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 and for 6 months after last dose of study drug(s).

- Condom with spermicide

and one of the following:

- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- 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.
- Vasectomized 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 (e.g., Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Hormonal shot or injection (eg, Depo-Provera) + male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system -Mirena®)
- + male condomNorelgestromin/ethinyl estradiol (EE) transdermal system + male condom with

spermicide

- Intravaginal device + male condom with spermicide (e.g., EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

Lactation
Lactation is an Exclusion Criterion within the study protocols for olaparib. It is not known whether olaparib is excreted in human milk.

Pregnancy
All outcomes of pregnancy should be reported to AstraZeneca.

Maternal exposure
If a patient becomes pregnant during the course of the study olaparib should be discontinued immediately.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day** i.e., immediately but no later than

the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

Paternal exposure
Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

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 bid (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply. For other overdoses, reporting should be done within 30 days.

e. **Metabolism and Drug Interactions**

The use of any natural/herbal products or other "folk 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 eCRF.

Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In

vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following strong inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known strong inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, idinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

For patients taking any of the above, the required wash-out period prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following strong CYP3A4 inducers should be avoided:

- Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitol, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting olaparib are:

- phenobarbitol 5 weeks, and for any of the others, 3 weeks.

After randomization, if the use of any strong inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Other Concomitant Medications
Any medications, other than those listed as excluded therapies, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF.

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.
.
Live virus and 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 are unknown.

Anticoagulant Therapy: Patients who are 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. Subcutaneous heparin is permitted.

AC-1.3.2 AZD5363

AZD5363 is a potent inhibitor of AKT 1, 2 and 3 (half maximal inhibitory concentration of the drug [IC50] <10 nM). Non-clinical in vitro and in vivo assays have demonstrated inhibition of phosphorylation of the AKT substrates GSK3β and PRAS40, tumor cell proliferation and xenograft tumor growth models. With treatment of nude mice bearing BT474c xenografts there was time- and dose-dependent inhibition of phosphorylation of the AKT substrates PRAS40 and GSK3β, and the downstream biomarker S6, after single oral doses of 100 and 300 mg/kg. Chronic oral treatment of nude mice bearing a variety of established and primary xenografts with AZD5363, resulted in dose-dependent tumor growth inhibition.

Secondary and Safety Pharmacology studies have been carried out to investigate the effects of AZD5363 on related and unrelated receptors and enzymes, the cardiovascular, central and peripheral nervous, respiratory, gastrointestinal and renal systems. The key findings were that:

- In a panel of 333 in vitro radioligand binding and enzyme assays, there were 8 targets at which there was significant activity.
- AZD5363 produced motor-related effects (reduction in spontaneous activity and touch response) at 4 hours post-dose. The no observed effect level (NOEL) was 30 mg/kg.
- AZD5363 was active at the human Ether-a-go-go-related Gene (hERG)-encoded potassium channel with an IC50 of 73 μM, and is classified as a low risk of triggering the QT-associated arrhythmia of Torsades de Pointes (TdP).
- In the dog telemetry study, heart rate was decreased for up to 8 hours following a single dose of 5, 30 and 40 mg/kg. At 30 mg/kg and 40 mg/kg there were peak decreases in systolic and diastolic blood pressure recovering within 4 hours, plus a sustained prolongation of QT interval corrected for heart rate using an individual linear regression formula (QTcR) and increase in integrated measure of left ventricular contractility (LVdP/dt+), along with elevation of both glucose and insulin levels. Intravenous (IV) administration of atenolol or verapamil 4 hours

post administration of AZD5363 reversed the effect on QTcR and LVdp/dt+. The no observed adverse effect level (NOAEL) is considered to be 5 mg/kg.

- AZD5363 had no effects on respiratory parameters following a single dose. The NOEL was 150 mg/kg.
- AZD5363 caused a dose-dependent, inhibition of gastric emptying at 100 mg/kg and 150 mg/kg. In addition, there was a decrease in intestinal transit at 150 mg/kg only. The NOEL was 30 mg/kg.
- In an assessment of renal function following a single oral dose, a marked glycosuria was seen at 100 mg/kg and 150 mg/kg, with concurrent diuresis. There was an increase in the fractional excretion of sodium and chloride at all doses, and of potassium and phosphate at 100 mg/kg and 150 mg/kg. The plasma concentration of phosphorous was slightly increased after 150 mg/kg, while the potassium concentration was slightly decreased after 100 mg/kg and 150 mg/kg. A NOEL could not be determined.

Investigators should refer to the latest IB for AZD5363 for safety information and findings from on-going trials.

Pharmacodynamics

- Platelet rich plasma (PRP) assays for GSK3β and PRAS40 phosphorylation showed a dose dependent inhibition of AKT substrate phosphorylation in Phase 1 patients following an acute dose of AZD5363.
- Phosphorylated PRAS40 (pPRAS40) was measured in the epithelial cells of the eyebrow hair root bulb and showed a trend for reduced PRAS40 phosphorylation with increasing AZD5363 exposure.
- Results from tumor samples from patients showed target engagement and inhibition of AKT substrate phosphorylation after exposure to AZD5363 at the recommended Phase 2 dose and schedule (480mg bid 4d on 3d off).

Please refer to the Investigator's Brochure (IB) for additional information regarding AZD5363.

a. **Formulation**

Laboratory code: AZD5363

CAS No.: 143532-39-1

Molecular formula: C21H25ClN6O2

Relative molecular mass: 428.92

b. **Dosage, Administration, and Storage**

The drug product is presented for oral administration as a beige film-coated tablet containing 80 mg and 200 mg of AZD5363. AZD5363 tablets are packed in high-density polyethylene (HDPE) bottles. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence.

AZD5363 beige film-coated tablets contain AZD5363, microcrystalline cellulose, mannitol, croscarmellose cellulose and magnesium stearate. The tablet film-coat contains polyvinyl alcohol,

titanium dioxide, polyethylene glycol, talc, yellow iron oxide, red iron oxide and black iron oxide.

The results of the effects of food on AZD5363 dosing indicate that the presence of food may reduce the rate of absorption of AZD5363, but the extent of absorption appeared to be comparable. The clinical relevance of this food effect is currently unknown, but a conservative approach has been taken to recommend that the existing food restrictions are maintained (ie, patients to fast from 2 h before dosing to 1 h after dosing, where possible) in ongoing clinical studies.

AZD5363 tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled in the study miss a scheduled dose or need to modify the timing of a scheduled dose for any reason, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours before or after the scheduled dose time. The dose should not be taken more than 2 hours in advance of the scheduled dose time. If greater than 2 hours has passed after the scheduled dose time, the missed dose is not to be taken and the patient should take the allotted dose at the next time schedule. Doses should not be taken fewer than 10 hours apart.

Storage
The product should be stored in the pack provided and used according to the instructions on the label.

c. Dosage Modification

Toxicities will be evaluated utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

The administration of AZD5363 may be delayed to assess or treat adverse events (AEs). Once a dose level reduction has occurred, the dose level may not be re-escalated.

Dose Modifications Due to Hematologic Toxicity
Dose modifications on Day 1 of each cycle will be based on blood counts determined on the day of scheduled treatment. Nadir blood counts will not be used to determine dose modifications. Treatment on Day 1 of any cycle will proceed if blood counts demonstrate absolute neutrophil count (ANC) ≥ 1500/μL, hemoglobin (Hgb) ≥ 10 g/dL, and platelets ≥ 100,000/μL.

AC-Table 2: Dose Modifications for Hematologic Toxicity

Day 1 Blood Counts	Olaparib	AZD5363
ANC ≥1500/ul; Hgb ≥10 g/dl; Platelets > 100,000ul	**No dose modification**	**No dose modification**
ANC <1500/ul or Hgb < 10 g/dl or Platelets < 100,000ul 1st incidence	**No dose modification**	**560 mg bid 2/7**
ANC <1500/ul or Hgb < 10 g/dl or Platelets < 100,000ul 2nd incidence	**No dose modification**	**480 mg bid 2/7 days**
ANC <1500/ul or Hgb < 10 g/dl or Platelets < 100,000ul 3rd incidence	**Discontinue treatment**	**Discontinue treatment**
	Neutropenic fever (ANC < 1,000/ul +Temperature > 101˚ F (38.5˚ C)	
1st incidence	**Delay until episode resolves with treatment. Resume at a dose of 300mg bid**	**Delay until episode resolves with treatment. Resume at a dose of 560mg bid 2/7 days**
2nd incidence	**Discontinue treatment**	**Discontinue treatment**

ANC = absolute neutrophil count; PO = orally.
Note: AZD5363 and olaparib should be discontinued if hematologic toxicity does not resolve (ANC ≥ 1500/µL, Hgb ≥ 10 g/dL, and platelets ≥ 100,000/µL) within 14 days.

Dose Modifications Due to Non-Hematologic Toxicity

AC-Table 3: Dose Modifications for Non-Hematologic Toxicity

CTCAE Grade	Action	Olaparib dose reduction	AZD5363 dose reduction
Grade 1-2 (tolerable)	Maintain Dose	No dose modification	No dose modification
Grade 2 (intolerable) or Grade 3			
1st Appearance	Hold until recovery ≤ Grade 1, then resume with recommended dose modifications	No dose modification	560 mg bid 2/7 days
2nd Appearance	Hold until recovery ≤ Grade 1, then resume with recommended dose modifications	No dose modification	480 mg bid 2/7 days
3rd Appearance	Discontinue treatment	Discontinue treatment	Discontinue treatment
Grade 4			
1st Appearance	Hold until recovery ≤ Grade 1, then resume with recommended dose modifications	No dose modification	560 mg bid 2/7 days
2nd Appearance	Discontinue treatment	Discontinue treatment	Discontinue treatment

CTCAE = Common Terminology Criteria for Adverse Events.

If Grade 3 or 4 non-hematologic toxicity (other than nausea, vomiting) occurs, treatment with AZD5363 and olaparib should be held. Treatment with AZD5363 and olaparib should be resumed according to Dose Modifications for Non-Hematologic Toxicity as soon as the toxicity resolves.

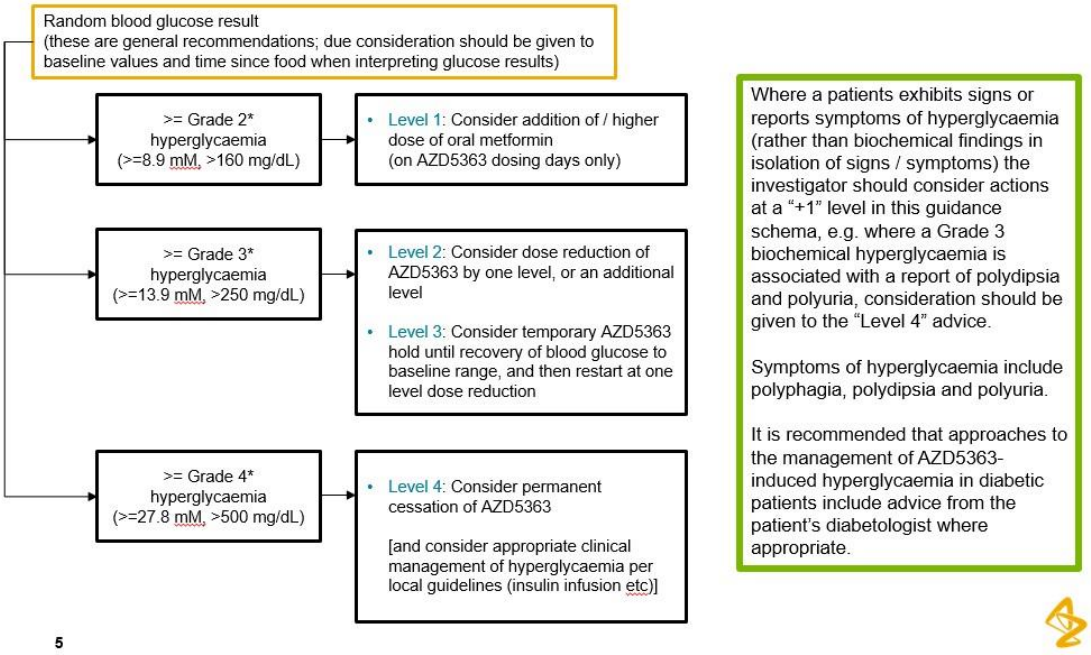
Glucose homeostasis

Hyperglycemia (defined in the clinical studies as at least 1 post-baseline laboratory report of glucose > ULN) is a frequent clinical observation, but is transient and reversible on cessation of treatment. The overall incidence of hyperglycemia is 94.8% across all the clinical trials to date. The majority of cases occurred within the first week of study treatment (91.1% in patients treated with AZD5363 monotherapy using intermittent dosing and 89.3% in patients treated with AZD5363 with paclitaxel). Approximately a third of patients with elevated glucose levels received metformin (given at the discretion of the investigator). A relationship between exposure to AZD5363 and HbA1c was investigated but no apparent linkage was seen between an individual's maximum HbA1c value and their maximum observed blood glucose value (either for random/non-fasting or fasting glucose). Therefore, even though AZD5363 is known to affect pathways of glucose metabolism and insulin signaling, there is no evidence from the present clinical studies for these transient hyperglycemic episodes to have an effect on HbA1c levels. In the clinical studies to date patients with proven diabetes have been excluded. However, the option to include patients with diabetes managed by diet alone is currently under consideration for future studies.

In order to reduce the potential risk of exacerbating abnormal glucose profiles, patients with Type I or Type II diabetes mellitus (irrespective of management) have been excluded from clinical studies with AZD5363 to date. However, given the apparent absence of clinical sequelae following AZD5363-induced hyperglycemia, 1 investigator sponsored study (A Phase 1b study of the oral PARP inhibitor olaparib with the oral mTORC1/2 inhibitor AZD2014 or the oral AKT inhibitor AZD5363 for recurrent endometrial, triple negative breast, and ovarian, primary peritoneal, or fallopian tube cancer), run by The University of Texas MD Anderson Cancer Center, Houston, USA, plans to include patients with Type II diabetes who are well controlled by diet alone. As our experience increases in this regard it may be that further modifications to the inclusion of such patients will become appropriate. Glucose profiles should be performed at the relevant time points in AZD5363 studies to adequately characterize emergent hyperglycemia and to allow appropriate clinical management of patients. A suggested algorithm for the management of hyperglycemia is provided. In addition, because of the pharmacological activity of AZD5363 on glycolysis and insulin signaling, fasting lipid profiles (triglycerides, high density lipoprotein, low density lipoprotein and cholesterol) will also be monitored at appropriate intervals.

Guidance on metformin use is included in the suggested hyperglycemia management algorithm.

AC-Figure 2: AZD5363 Glucose Management



*These grade thresholds based on CTCAE cut-offs for fasting glucose, but applied to random glucose here.

Diarrhea and Rash

Rash is a frequent clinical observation, with 52.6% patients in all the clinical studies reporting rash. The occurrence of rash is less marked in terms of incidence and severity with intermittent dosing. 9.8% of patients reported rash of Grade 3 or above (all cases considered by the investigator to be drug-related). Eight out of the 102 patients with rash (7.8%) had events that were considered serious and 8 patients discontinued AZD5363 treatment due to rash. Eight patients had a DLT of rash. Twelve patients (11.8%) had their dose of study medication interrupted and 10 patients (9.8%) had the dose reduced due to rash. In 57.8% of patients the rash resolved before cessation of study treatment, with treatment for the rash being required in 64.7% of cases.

The onset of rash typically occurs after the first week of AZD5363 treatment and resolves with dose interruption. Grade 3 rash leading to discontinuation of AZD5363 occurred in 4.1% of patients. The vast majority of patients subjected to re-challenge following resolution of rash suffered a recurrence of the toxicity. There are no standard exclusion criteria for patients with rash. Clinical experience indicates that rash can be managed with treatment as outlined in the rash management algorithm (eg, use of oral or topical steroids, use of oral antihistamine), as well as by interruptions to AZD5363 dosing.

Diarrhea is a frequent clinical observation in studies with AZD5363, with most cases starting within the first week of treatment. Overall, 73.7% patients in all the clinical studies had diarrhea. Overall, 14.9% of patients had diarrhea of Grade 3 or above (in all but 3 patients who had ≥Grade 3 diarrhea the events were considered by the investigator to be drug-related). Thirteen of the 145 patients with diarrhea (9.0%) had events that were considered serious, with 7 patients discontinuing study treatment as a result of diarrhea. Five patients had a DLT of diarrhea. Twenty patients (13.8%) had their dose of study medication interrupted and 9 patients (6.2%) had their dose reduced due to diarrhea. In 67.3% of patients the diarrhea resolved before cessation of study treatment, with treatment for the diarrhea being required in 71.7% of patients.

Most patients report diarrhea within the first week following commencement of AZD5363 dosing. Most patients experience 1 or 2 episodes, however, patients receiving AZD5363 in combination with paclitaxel seemed to experience more episodes. There appeared to be a relationship between increasing dose and severity with continuous monotherapy of AZD5363, but this was not seen with the intermittent dosing schedules. Patient reports of diarrhea are to be evaluated and treated by investigators according to local practice (eg, use of medications such as loperamide). The need for an interruption in dosing with AZD5363 should be considered according to the clinical study protocol.

Hypersensitivity

Hypersensitivity has been commonly (4 /301 patients) reported within the AZD5363 program. Symptoms of hypersensitivity included rash in association with 1 or more of events such as flushing, pruritus, urticaria, throat itchiness, pyrexia and facial and/or lip edema. Time to onset of event ranged from 11 to 120 days (median: 21 days) from start of therapy with AZD5363. In all patients hypersensitivity or related events were considered related to AZD5363 by the investigator and in 3 patients the reported events were considered serious, leading to hospitalization or prolonged hospitalization. Three patients had positive re-challenge. One patient had a reported allergy to heat and cold. In all patients the symptoms resolved with study drug discontinuation and treatment with antihistamines and steroids.

Patients with history of hypersensitivity to active or inactive excipients of AZD5363 or drugs with a similar chemical structure or class to AZD5363 will be excluded from studies. Significant hypersensitivity reactions, as characterized by rash along with clinical features such as flushing, pruritus, urticaria, throat itchiness, pyrexia and facial and/or lip edema requiring treatment with antihistamines and steroids have occurred commonly (1-10%) in patients receiving AZD5363. In the case of hypersensitivity reactions, AZD5363 should be discontinued and symptomatic/supportive

therapy should be initiated (including with antihistamines and/or steroids) as considered appropriate by the investigator/treating physician. Any subsequent decision on re-challenge with AZD5363 at the same or a lower dose, with its potential for recurrence of such or more severe events should be carefully considered against the potential benefits to the individual patient from continuation of AZD5363 therapy.

AC-Table 4: Summary of guidance on dose adjustments of AZD5363 for toxicity

Toxicity	AZD5363
Diarrhea of CTCAE Grade ≥3 or that is clinically significant or intolerable and causally related to treatment with AZD5363/matching placebo.	Institute appropriate anti-diarrheal treatment. (Refer to **"Guidance for the Management of Adverse Events in Studies of AZD5363**" for treatment guidance). If clinically appropriate or if toxicity does not improve to CTCAE Grade ≤ 2 or remains clinically intolerable, despite optimal treatment, withhold AZD5363/matching placebo for up to 14 days. If toxicity improves to CTCAE Grade ≤2 or becomes clinically tolerable reinstate AZD5363/matching placebo, as clinically appropriate, at either the current dose or at a reduced dose (1 dose level) maintaining treatment for toxicity as necessary. Where a CTCAE Grade ≥3 or clinically significant or intolerable toxicity does not improve after 14 days of AZD5363/matching placebo dose interruption, AZD5363/matching placebo should be permanently discontinued. Recurrence: on recurrence of a CTCAE Grade ≥3 or clinically significant or intolerable toxicity, reinstate treatment as required. If toxicity improves to CTCAE Grade ≤2 or becomes clinically tolerable reinstate AZD5363/matching placebo, as clinically appropriate, at either the current dose or at a reduced dose (up to two dose level reductions) maintaining treatment for toxicity as necessary. If toxicity does not improve to CTCAE Grade ≤2 or remains clinically significant or intolerable, despite optimal treatment, withhold dose for up to 14 days until improvement of toxicity.
Any skin reaction of CTCAE Grade ≥ 3 or that is clinically significant or intolerable and causally related to treatment with AZD5363/matching placebo	For any skin reaction that is CTCAE Grade ≥3 or clinically significant or intolerable withhold dose for up to 14 days until improvement of toxicity. If toxicity improves to CTCAE Grade ≤1 within 14 days reinstate AZD5363/matching placebo at the current dose maintaining treatment for toxicity as necessary If toxicity improves to CTCAE Grade 2 within 14 days reinstate AZD5363/matching placebo at a reduced dose (1 dose level) maintaining treatment for toxicity as necessary Where a CTCAE Grade ≥3 or clinically significant or intolerable toxicity does not improve to a lower CTCAE Grade within 14 days of AZD5363/matching placebo dose interruption, AZD5363/matching placebo should be permanently discontinued.

Stomatitis

Stomatitis is a very common clinical observation, affecting 32 patients (14.0%) in AZD5363 intermittent monotherapy, 10 patients (26.3%) in combination with paclitaxel, and 2 patients (7.7%) in combination with fulvestrant.

In AZD5363 intermittent monotherapy, the majority of stomatitis AEs were Grade 1 or 2 (91.4%), and the maximum severity of AEs experienced by patients was CTCAE Grade 3 (8.6%). There were 3 AEs leading to dose interruption, and of these, all resulted in a positive de-challenge, and in the 2 patients subsequently re-administered the study drug, both received a reduced AZD5363 dose and both experienced negative re-challenge. The median duration of all AEs was 15 days.

Dry skin

Dry skin is a very common clinical observation, affecting 27 patients (11.8%) in AZD5363 intermittent monotherapy, 6 patients (15.8%) in combination with paclitaxel, and 1 patient (3.8%) in combination with fulvestrant.

In AZD5363 intermittent monotherapy, the majority of dry skin AEs were Grade 1 (92.9%), and the maximum severity of AEs experienced by patients was CTCAE Grade 2 (7.1%). There were no AEs leading to dose interruption, reduction, or study discontinuation. The median duration of all AEs was 91.5 days.

Pruritus

Pruritus is a common clinical observation, affecting 21 patients (9.2%) in AZD5363 intermittent monotherapy group, 7 patients (18.4%) in combination with paclitaxel, and none in combination with fulvestrant.

In AZD5363 intermittent monotherapy, the majority of pruritus AEs were CTCAE Grade 1 or 2, and 1 AE was Grade 3. There were no AEs leading to dose interruption or study discontinuation. The median duration of all AEs was 37 days. Cardiovascular effects

In all patients, cardiac function will be monitored regularly throughout the study. Heart rate, electrolytes (sodium, chloride, potassium and bicarbonate), ECG measurements, systolic and diastolic blood pressure will be monitored prior to and 1, 2, 6 and 24 hours following administration of AZD5363, then weekly during the first cycle (labs and blood pressure pre-dose and ECG assessments up to 6 hours post-dose), at the start of each subsequent cycle thereafter (labs and blood pressure pre-dose and ECG assessments up to 6 hours post-dose) and at discontinuation. Troponin I or T will be monitored prior to administration of AZD5363, weekly during the first cycle, at the start of each subsequent cycle and at discontinuation. In addition, a MUGA scan or echocardiogram to assess LVEF will be conducted at screening, and as clinically indicated as management of AEs.

d. **Metabolism and Drug Interactions**

In vivo experiments indicate that AZD5363 is a time-dependent inhibitor of CYP3A4, which may result in increased exposure of drugs metabolized via CYP3A4 and with the potential to increase the toxicity of these drugs when co-administered with AZD5363. AZD5363 is itself a substrate of CYP3A4 although data available to date suggests that glucuronidation may be the major metabolic route. Co-administration of CYP3A4 inhibitors may increase exposure to AZD5363 and hence potentially affect efficacy/toxicity, and hence increase the risk of time-dependent inhibition (and resultant toxicity of CYP3A4 substrates). In addition, co-administration of CYP3A4 inducers may decrease the exposure to AZD5363 and may potentially affect efficacy. AZD5363 is also a moderate inhibitor of CYP2D6 *in*

vitro. This may increase the exposure of drugs metabolized via CYP2D6 with the potential to increase the toxicity of these drugs when co-administered.

Use of strong inhibitors or inducers of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort) should be avoided. A list of these drugs will be provided as an appendix to the clinical study protocols. All patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to potently modulate CYP3A4 enzyme activity from the time they enter the screening period until 2 weeks after the last dose of study treatment. All patients should avoid concomitant use of drugs and herbal supplements known to be CYP3A4 or CYP2D6 substrates from the time they enter the screening period until 2 weeks after the last dose of study treatment wherever possible. If co-administration is necessary for appropriate clinical care then additional monitoring for signs of toxicity related to increased exposure to the substrates may be required. A list of these drugs will be provided as an appendix to the clinical study protocols.

Emerging *in vitro* data has revealed that AZD5363 has a potential to inhibit the OATP1B1 transporter. This transporter is implicated in the distribution and clearance of many of the statins. Of the statins that are minimally affected by CYP3A4 inhibition, rosuvastatin and pravastatin (but not fluvastatin) can be affected by OATP1B1 inhibition. In an assessment of the potential for AZD5363 to inhibit OATP1B1 based on the *in vitro* signal, the AUC of these drugs may be increased by 1.3-fold for pravastatin and 1.5-fold for rosuvastatin (static assessment based on maximal free liver inlet concentration of AZD5363). As a conservative response to this emerging data it is recommended that doses of rosuvastatin be capped to 10 mg once daily and pravastatin to 40 mg once daily when combined with AZD5363, and for a 2-week period before and after AZD5363 treatment.

Drugs affecting CYP3A4 metabolism that AstraZeneca strongly recommend are not combined with AZD5363

There are currently no data confirming that there are any pharmacokinetic (PK) interactions between any agents and AZD5363. The potential interactions detailed below are considered on the basis of the preclinical data only. The following lists are not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

AC-Table 5 CYP3A4 potential interactions with AZD5363

(1) Strong CYP3A4 inhibitors that may increase exposure to AZD5363 more than 5-fold

Ketoconazole Protease inhibitors (danoprevir, ritonavir, saquinavir, indanavir, tapranavir, telaprevir, elvitegravir, lopinavir, nelfinavir, bocepravir) Cobicistat Conivaptan Nefazodone Mebefradil	Minimum of 2 weeks washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363

Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin Troleandomycin	Minimum of -week washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363

(2) Strong Inducers of CYP3A4 that may reduce exposure to AZD5363 by more than 5-fold

Phenobarbital Carbamazepine Phenytoin Rifampicin Rifabutin Mitotane Enzalutamide	Minimum of 2-weeks washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363
St John's Wort	Minimum of 3-weeks washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363

(3) Drugs affecting CYP3A4 metabolism that AstraZeneca considers may be allowed with caution.

Moderate Inhibitors of CYP3A4 that may increase exposure to AZD5363

Diltiazem Verapamil Erythromycin Fluconazole Aprepitant	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD5363.
Grapefruit juice Seville oranges (and other products containing Seville oranges)	Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily).

(4) Medicines that are significantly metabolized by CYP3A4 that AstraZeneca strongly recommend are not combined with AZD5363

There are currently no data confirming that there are any pharmacokinetic (PK) interactions between AZD5363 and the following CYP3A4 substrates. The potential interactions detailed below are considered on the basis of the preclinical data only. The following list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to be sensitive to CYP3A4 inhibitors. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Exposure, pharmacological action and toxicity that may be increased by inhibition of CYP3A4 by AZD5363

Alfentanil Cyclosporin Diergotamine Ergotamine Fentanyl Sirolimus Tacrolimus Atorvastatin Lovastatin Simvastatin Cerivastatin	Minimum of 1 week washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363
Carbamazepine	Minimum of 2 weeks washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363.

(5) Medicines that are significantly metabolized by CYP3A4 that AstraZeneca considers may be allowed with caution

Exposure, pharmacological action and toxicity that may be increased by inhibition of CYP3A4 by AZD5363

Erythromycin Trazodone Tamoxifen Alprazolam Midazolam Triazolam Felodipine Isradipine Nifedipine Methylprednisolone Pimozide Quinidine Domperidone	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD5363.

AC-Table 6: CYP2D6 potential interactions with AZD5363

(1) Agents that are sensitive to CYP2D6 inhibition that AstraZeneca strongly recommends are not combined with AZD5363

There are currently no data confirming that there are any pharmacokinetic (PK) interactions between AZD5363 and the following CYP2D6 substrates. The potential interactions detailed below are considered on the basis of the preclinical data only. The following list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to be sensitive to CYP2D6 inhibitors. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Exposure, pharmacological action and toxicity that may be increased by inhibition of CYP2D6 by AZD5363	
Amitryptyline Desipramine Trimipramine Doxepin	Minimum of 2-weeks washout prior to AZD5363 administration and for 2- weeks following discontinuation of AZD5363
Atomoxetine Metoprolol Nefazodone Nebivolol Perphenazine Tropisetron Tolterodine	Minimum of 1-week washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363

(2) Agents that are sensitive to CYP2D6 inhibition that AstraZeneca considers may be allowed with caution

Exposure, pharmacological action and toxicity that may be increased by inhibition of CYP2D6 by AZD5363	
Venlafaxine Paroxetine Fluoxetine	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD5363.

(3) Agents that are sensitive to combined CYP3A4 and CYP2D6 inhibition that AstraZeneca strongly recommend are not combined with AZD5363

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between AZD5363 and the following agents; a potential interaction is considered on the basis of the preclinical data only. This list is not intended to be exhaustive, and a similar restriction will apply to other agents with narrow therapeutic windows that are known to depend on combined CYP3A4 and CYP2D6 metabolism. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

AC-Table 7: Other potential interactions with AZD5363

(1) Exposure, pharmacological action and toxicity that may be increased by inhibition of CYP3A4 and CYP2D6 by AZD5363

Haloperidol	Minimum of 2-weeks washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363
Tramadol	Minimum of 1-week washout prior to AZD5363 administration and for 2 weeks following discontinuation of AZD5363

(2) Guidance for drugs that are that are significantly metabolized by CYP2B6, CYP2C9 or CYP2C19 and have a narrow therapeutic margin that AstraZeneca considers may be allowed with caution

Weak signals for competitive inhibition of CYP2B6, CYP2C9 and CYP2C19 cytochrome P450 activities have been demonstrated by in vitro laboratory investigations. There are currently no data confirming that there is a pharmacokinetic (PK) interaction between AZD5363 and substrates of these isoforms; a potential interaction is considered on the basis of the preclinical data only. The following list is intended to identify known sensitive substrates of CYP2B6, CYP 2C9 and CYP 2C19 that have a narrow therapeutic margin. The list is not intended to be exhaustive, and a similar restriction should be applied to any other sensitive substrate with narrow therapeutic margin. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Exposure, pharmacological action and toxicity that may be increased by inhibition of CYP2B6, CYP2C9 and CYP2C19 by AZD5363

<u>CYP2B6</u> Bupropion <u>CYP2C9</u> Warfarin <u>CYP2C19</u> Clobazam	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD5363.

AC-1.4 CONCOMITANT AND EXCLUDED THERAPIES

AC-1.4.1 Concomitant Therapy

Refer to the main body of the protocol (Concomitant and Excluded Therapies) for concomitant therapies allowed.

Palliative radiotherapy
Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF. Study treatment should be discontinued for a minimum of 3 days before the patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

AC-1.4.2 Excluded Therapy

The following restrictions apply during the entire duration of study treatment:

- No other investigational therapy should be given to patients.
- No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, herbal therapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial. The patient can receive a stable dose of corticosteroids during the study if these were started at least 4 weeks prior to treatment, as per exclusion criteria. Bisphosphonates and Denosumab for bone metastases are allowed if these were started at least 4 weeks prior to treatment with study drug. Octreotide is allowed if dose is stable for >3 months with no worsening of carcinoid syndrome. Hormonal therapy with luteinizing hormone-releasing hormone (LHRH) analogues for medical castration in patients with castrate-resistant prostate cancer are permitted. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics if no evidence of disease progression is present.
- Live virus and bacterial vaccines should not be administered whilst 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 are unknown.
- Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days after the last dose of study medication.

AC-1.5 STUDY ASSESSMENTS

	Screening	Day 1 of Cycle 1	C1D8 C1D15 C1D22	Day 1 of each cycle[o]	Every 8 weeks	End of Study	30 Day Follow-up	Long term follow up as per main protocol
Visit window (days)	28[m]	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 7	+/- 7
Informed consent	X							
Inclusion/Exclusion Criteria	X							
Pregnancy Test[a]	X	X						
Molecular Selection of Patients based on Archival Tumor Tissue (Paraffin	X							
Medical History	X							
Physical examination, weight and vital signs [b]	X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X	X	X	X	
Laboratory tests (Clinical Chemistry/hematology/urinalysis /coagulation)[c]	X	X[l]	X	X		X[d]		
Glucose, Insulin	X	X		X[e]		X[d]		
Concomitant medications	X	X		X		X		
Dosing compliance		X		X		X		
Adverse events	X	X		X	X	X	X	
Echocardiology/MUGA[f]	X							
ECG[g]	X	X	X	X[h]		X		
RECIST Assessments [i]	X				X	X	X	
Tumor Tissue (Paraffin embedded) (optional)[j]		X				X		
Plasma Sample[k]		X			X	X		
Anti-cancer therapy follow-up								X

a Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. 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.

b A complete physical examination will be performed at the following timepoints (within 24 hours of visit): 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). Vital signs (heart rate, systolic and diastolic blood pressure, oxygen saturation (pulse oximetry), respiration rate, weight, height (at screening) and temperature)

Heart rate and systolic and diastolic blood pressure will be monitored prior to and 1, 2, 6 and 24 hours following C1D1, on pre-dose on cycle 1 day 8, on cycle 1 day 15, and on cycle 1 day 22. In all other cycles at pre-dose on day 1, and then at discontinuation.

c 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 thromboplastin 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. If APTT testing is not locally available, Partial Thromboplastin Time (PTT) testing may be done along with INR. Any clinically significant results on PTT will be confirmed with APTT.

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 AstraZeneca Patient Safety 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.

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

Biochemistry assessments for safety (sodium, chloride, potassium, bicarbonate, 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]).

Laboratory tests to also include Hgba1c, triglycerides and cholesterol·

Cardiac markers CK, CK-MB, Troponin (isoform as per institutional norm), LDH and AST should be assessed at screening and pre-dose on first day of treatment.

Troponin (additionally other cardiac markers, i.e. CK, CK-MB, AST and LDH depending on the investigators decision if clinically indicated) should also be assessed on identification of abnormal ECG findings, e.g. new repolarization abnormalities, found to be possibly clinically significant by investigators judgment. A repeat cardiac marker assessment should also be performed 24 hours later if such changes have been observed. The same Troponin isoform should be assessed at each of the visits.

Troponin will be monitored routinely pre-dose on cycle 1 day 1, on cycle 1 day 8, on cycle 1 day 15, and on cycle 1 day 22. In all other cycles at pre-dose on day 1, and then at discontinuation.

Sodium, chloride, potassium and bicarbonate will be monitored prior to and 1, 2, 6 and 24 hours following C1D1, and pre-dose on cycle 1 day 8, on cycle 1 day 15, and on cycle 1 day 22. In all other cycles at pre-dose on day 1, and then at discontinuation.

An unscheduled serum urea and creatinine test should be performed in every case of an SAE of diarrhea.

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.
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 G 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

There is a 48 hr window for performance of lab testing for each visit

d 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.

e Glucose and insulin will be checked at screening, baseline, and on day 1 (pre-, 2-4 hours post-) of each cycle. Note that

this glucose monitoring is in addition to the usual laboratory monitoring stated in c.

f Echocardiography will also be carried out if a patient develops signs and/or symptoms suggestive of a deterioration in left ventricular function or in case of the pre-specified ECG finding such as T-wave inversions.

Echocardiography should include assessment of left ventricular end-systolic volume, left ventricular end-diastolic volume and LVEF. If an Echocardiography scan cannot be taken a MUGA scan to assess left ventricular ejection fraction (LVEF) will be conducted. The modality of the cardiac function assessments must be consistent within patient, ie, if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patient should also be examined using the same machine and operator throughout the study wherever possible. Other alternative methods of assessments could be used additionally if they are a part of the local standard of care, or if the investigator considers them necessary for the therapeutic management of the patient. Important cardiac symptoms should be reported as AEs/SAEs and should be carefully evaluated in regard to developing of acute or worsening of chronic cardiac failure, especially in anthracycline treated patients. Congestive cardiac failure should be treated and followed according to standard medical practice.

g Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. For each time point 3 ECG recordings should be taken one after another. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study.

If an abnormal ECG finding at baseline is considered by the investigator to be clinically significant, it should be reported as a concurrent condition. During the study, clinically significant abnormal ECG findings not present at baseline should be reported as an AE. If present, the clinical signs and symptoms associated with the abnormal finding should be reported as the AE with the ECG abnormality given as explanatory information.

Troponin (additionally other cardiac markers, i.e. CK, CK-MB, AST and LDH depending on the investigators decision if clinically indicated) should also be assessed on identification of abnormal ECG findings, e.g. new repolarization abnormalities. A repeat cardiac marker assessment should also be performed 24 hours later, if such findings occur the same Troponin isoform should be assessed at each of the visits.

An ECG should be performed at any cardiac event with symptoms that may be due to cardiac ischemia, or arrhythmia (such as chest pain or palpitations). An ECG will also be captured in all cases of dyspnea and pulmonary edema and additionally at the discretion of the investigator if clinically indicated.

h ECGs to be taken routinely on cycle 1 day1 pre-dose, 1 hr post dose, 2 hrs post dose, 6 hrs post dose, and 24 hrs post dose; on cycle 1 day 8 (up to 6 hrs post dose); on cycle 1 day 15 (up to 6 hrs post dose); and cycle 1 day 22 (up to 6 hrs post dose), Post dose ECGs may be taken at the time specified +/- 15 minutes. In all other cycles at pre-dose on day 1, and then at discontinuation.

i 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. 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).

j Tumor sample at baseline if feasible (optional). The sample can be collected up to 4 weeks before the first dose. Therefore, any sample collected during this time period prior to study enrollment can be used as baseline sample. The tumor sample for use in genetic and protein analyses should be formalin-fixed and embedded in paraffin according to standard procedures at each institution. Additional tumor samples may also be collected and used fresh or frozen.

Tumor sample at progression or discontinuation if feasible (optional). The sample can be collected at progression or discontinuation, or any time between progression and discontinuation from the study. The tumor sample for use in genetic and protein analyses should be formalin-fixed and embedded in paraffin according to standard procedures at each institution. Additional tumor samples may also be collected and used fresh or frozen

k Plasma samples (optional) will be collected at baseline, on treatment and at progression/ discontinuation on study to isolate ctDNA to determine the mutational profile and changes thereof. The plasma sample at baseline should can be collected up to 2 weeks before the first dose. Samples on study should be taken at the end of the first cycle (+/- 7 days),

and at the end of the cycles 4, 6 and 10 (+/- 7 days) and at progression or discontinuation or any time between progression and discontinuation from the study

Additional samples (optional) after cycle 10 and before progression can be collected, if the investigator deems a particular time point of interest. However, samples should not be collected more frequent than every 2 cycles. F describes the procedures for collection, processing, storage and shipment of plasma.

l Results of all cycle 1 day 1 laboratory tests must re-meet eligibility criteria

m: Screening to be performed within 28 days unless otherwise specified

o: Continuous use of Olaparib is suitable during this window

APPENDIX D: AZD6738 plus Olaparib in Patients with DNA Damage Repair Gene Mutations

Treatment of patients with solid tumors that harbor DNA damage repair gene mutations is part of the clinical trial outlined in the main protocol.

Defects in components of the HDR/DSB repair mechanism require affected cells to depend on alternative error-prone pathways of DNA repair, including BER and B-NHEJ. PARP1 hyperactivity has been demonstrated in HDR-defective cells and ought to confer a similar sensitivity to PARP inhibitors, which target the essential DDR pathway remaining intact in HDR deficient cells [45]. This has led to the concept of "*BRCA-ness*", which proposes that somatic mutations in the BRCA 1 and 2 genes, as well as other HDR genes as noted above, should confer a similar sensitivity to PARP inhibitors as gBRCA mutations. This expanded repertoire of mutations in HDR should be considered as potential clinical targets for DDR-focused therapies such as PARP inhibitors. This would include somatic mutations of BRCA 1 & 2, the BRCA interacting proteins of the MRN complex (MRE11, RAD 50, NBS), RAD51, PALB2/FANCN, FANCD2, FANCC and DSS1. This grouping of BRCA-interacting proteins can be considered the HR effector arm or RAD51 foci-forming proteins. Another grouping of DDR proteins includes the checkpoint controllers ATM, ATR, CHK1 and CHK2, which regulate cell all cycle and the expression of the HR effector proteins such as BRCA1. Other DDR proteins comprise the FANCA/B/C/E/F/G/L/M complex core, which activates FANCD2, thus localizing the HDR repair effector complex to the site of DSB and SSB, plays a critical role in DDR such that loss of any of the components has a profound repair-defective phenotype.

In 50 consecutive tumors profiled at Yale, nonsense mutations and mutations considered to have major effects on DNA damage repair pathways at critical functional sites (COSMIC) were detected in 8 (16%). This incidence makes identifying appropriate patients for this study feasible. These aberrations were detected in multiple different tumor types including GBM, H&N cancer, NSCLC, prostate, breast, colorectal and other solid and hematological malignancies.

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

Although ATM-deficient cells have a greater sensitivity to AZD6738, AZD6738 is cytotoxic in cell line panels of ATM-proficient hematological malignancies *in vitro*. In vivo combinations of AZD6738 with radiation induces a dose-dependent anti-tumor response, with regressions in ATM-deficient models and growth inhibition in ATM-proficient models. Anti-tumor activity of AZD6738 may, therefore, also be seen more broadly.

The combination of AZD6738 and olaparib are synergistically cytotoxic in HDR ovarian cancer cell lines in vitro and in vivo in a BRCA2$^{-/-}$ PDX model. PARP inhibition activates ATR/CHK1 as a survival mechanism and concurrent inhibition of this pathway permits the BRCA $^{-/-}$ cells to enter into mitotic catastrophe and apoptosis (B). The ATR-Chk1 checkpoint pathway serves to ensure cell survival after replication stress of many types, therefore a normal and robust checkpoint is thought to be a mechanism of resistance to chemotherapy.

This appendix contains details and study requirements that are specific to treatment with olaparib and AZD6738 including:

AD-1 MATERIALS AND METHODS

AD-1.1 PATIENTS

Eligible patients must meet all eligibility requirements contained in the main study protocol.

AD-1.1.1 Inclusion Criteria

Refer to the main protocol Inclusion Criteria.

AD-1.1.2 Additional Exclusion Criteria

Refer to the main protocol Exclusion Criteria.

AD-1.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (STUDY DESIGN AND RATIONALE).

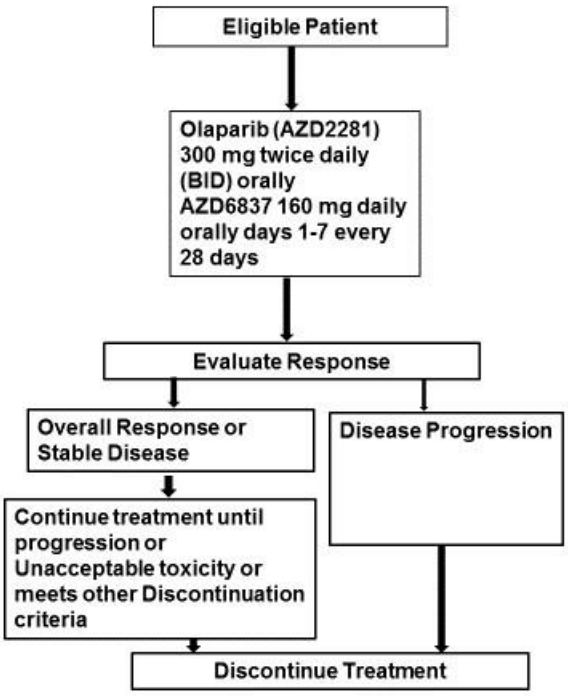
AD-1.3 STUDY TREATMENT

All patients will receive treatment with olaparib and AZD6738, given at a daily dose of AZD6738 160 mg orally (PO) daily between days 1-7 and bid daily dose of 300 mg orally (PO) in cycles of 28 days (4 weeks) duration. A schema of the study design is presented in Study Schema: AZD6738 and Olaparib.

All patients will receive:

- Olaparib 300 mg bid daily tablets.
- AZD6738 one 100mg and three 20 mg tablets
- No routine premedications are required.

AD-Figure 1: Study Schema: AZD6738 plus Olaparib



AD-1.3.1 Olaparib

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB)

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerization (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 DNA recombination repair (HDR). Tumors with HDR deficiencies, such as serous ovarian cancers, 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.

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. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

PARP inhibitors such as olaparib may also enhance the DNA damaging effects of chemotherapy.

For further information please refer to the current version of the olaparib IB.

a. **Formulation**

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

Laboratory Codes: AZD2281; KU-0059436; CO-CE 42

CAS No.: 763113-22-0

Molecular Formula: C24H23FN4O3

Molecular Weight: 434.46

b. Dosage, Administration, and Storage

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the investigator as round or oval *green film coated tablets*

AD-Table 1: Olaparib dosage form and strength

Investigational product	Dosage form and strength
Olaparib	*100 mg tablet*
Olaparib	*150 mg tablet*

Descriptive information for olaparib can be found in the Investigator's Brochure

For all centers, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 32 tablets and desiccant. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Olaparib will be dispensed to patients on Day 1 of each cycle until the patient completes the study, withdraws from the study or closure of the study.

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all remaining tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g. forgetting to take the tablets or vomiting) or need to modify the timing of a scheduled dose for any reason, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. The dose should not be taken more than 2 hours in advance of the 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. Doses should not be taken fewer than 10 hours apart

Combination drug should be given at least 1 hour after the patient has taken their olaparib morning dose.

Food intake restrictions

Olaparib doses can be taken without regard to food. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided

Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The product should be stored in the pack provided and used according to the instructions on the label.

Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.

Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrolment code (E-code) to be completed at the time of dispensing.

The label will include the following information:

- blank lines for quantity of tablets to be taken
- enrolment code (E-code)
- date of dispensing
- Instructions stating that the olaparib tablets should be taken at approximately the same time each morning and evening

c. Dosage Modification

Dose reduction for AZD6738 and olaparib

Toxicities will be evaluated utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

AD-Table 2: Guidance for dose reductions for AZD6738 and olaparib

Dose Level	AZD6738	Olaparib
Initial dose level	160 mg QD Days 1-7	300 mg BID Days 1-28
1st dose reduction	Dose reduce either AZD6738 or Olaparib or Both	
Hematological Toxicity	160mg QD Days 1-4	250 mg BID Days 1-28
Non-Hematological Toxicity	120mg QD Days 1-7	250 mg BID Days 1-28
2nd dose reduction	Dose reduce either AZD6738 or Olaparib or Both	
	120 mg OD Days 1-4	200 mg BD Days 1-28
3rd dose reduction: No further reduction permitted, withdraw patient and treat as clinically indicated. Dose must not be re-escalated even if toxicities have resolved.		

Note: filgrastim or PEG-filgrastim may be used at the investigator's discretion

Management of hematological toxicity

At the first occurrence of CTCAE grade 3 and 4 hematological toxicity, AZD6738 and olaparib should be held until resolution of toxicity. At the resolution of the first occurrence of any of these toxicities, no

change must be made to the dose. The second occurrence, upon resolution of toxicity, AZD6738 and/or olaparib should be reduced by the 1st dose reduction for hematological toxicity to 160 mg qd for 4 days and/or 250mg bid q 12 hours daily(Table 3). At the third occurrence, AZD6738 and olaparib should be reduced by the 2nd dose reduction to 120 mg qd Days 1-4 and 200mg bid q 12 hours daily(Table 3). If despite these changes there is a fourth occurrence of toxicity, the patient should be withdrawn from the treatment. Please note that, for each dose reduction, the investigator may choose to reduce AZD6738 or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step. for simultaneous toxicities (for example, neutropenia and thrombocytopenia), if either AZD6738 and olaparib has been recently held or dose-reduced, and a second toxicity develops, 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, neutropenia followed by thrombocytopenia) should follow Table 4; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle. Refer to Table 3 and 4 for specific dose modification guidance regarding hematological toxicity.

AD-Table 3: Summary of guidance on the management of hematologic toxicity for AZD6738 and olaparib

Toxicity	AZD6738 and olaparib
Any hematologic toxicity (CTCAE grade ≥ 3)	1st occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue AZD6738 and olaparib. 2nd occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at 1st reduced dose level for hematological toxicity The investigator may choose to reduce AZD6738 or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step ir the toxicity recurs. If symptoms do not recover to ≤CTCAE grade 1, discontinue AZD6738 and olaparib. 3rd occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at 2nd reduced dose level for hematological toxicity. The investigator may choose to reduce AZD6738 or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step ir the toxicity recurs. If symptoms do not recover to ≤CTCAE grade 1, discontinue AZD6738 and olaparib. 4th occurrence Off-study

AD-Table 4: Neutropenia, Infection, Febrile Neutropenia Dose Modifications and Management

Toxicity	AZD6738 and olaparib
- Fever (≥101°F [38.5°C]) and/or systemic infection	Hold dose until recovery. Then, upon resuming dosing, reduce

Toxicity	AZD6738 and olaparib
- Grade 3 neutropenia (ANC ≥500 to <1000/μL) of any duration - Grade 4 neutropenia (ANC<500/μL >4 days) - Grade 3 thrombocytopenia (platelet count 25,000 to <50,000/μL) with bleeding	AZD6738 and olaparib to the next lower dose level[a].
Grade 4 febrile neutropenia or Grade 4 infection with neutropenia (both defined as septic shock) Thromboctyopenic hemorrhage (gross occult bleeding) associated with a platelet count <50,000/μL	Discontinue treatment and follow for disease progression.

Hematologic toxicity management guideline

Management of anemia

Adverse events of anemia CTCAE grade 1 or 2 (Hb ≥8 g/L) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anemia. Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. However, if a patient develops anemia CTCAE grade 3 (Hb <8 g/L) or worse, study treatment should be interrupted for up to maximum of 4 weeks. Study treatment can be restarted at the same dose if Hb has recovered to >9 g/L. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions

If a patient has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by investigator, study treatment should be interrupted as outlined in Table 3. Study treatment should be restarted at a reduced dose.

Management of neutropenia and leukopenia

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTC AE grade >1 (ANC > 1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If a patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

If a patient develops prolonged hematological toxicity such as:

≥2 week interruption/delay in study treatment due to CTC 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. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to 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 an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if diagnosis of MDS and/or AML is confirmed.

Management of non-hematological toxicity

For non-hematological toxicity, upon resolution of toxicity, AZD6738 and/or olaparib may be reduced by the 1st dose reduction to 120 mg QD Days 1-7 and/or 250 mg BID Days 1-28At the first occurrence of CTCAE grade 3 and 4 non-hematological toxicity, AZD6738 and olaparib should be held until resolution of toxicity. At the resolution of the first occurrence of any of these toxicities, no change must be made to dose. At the second occurrence, upon resolution of toxicity, AZD6738 and/or olaparib should be reduced by the 1st dose reduction for non-hematological toxicity to 120 mg qd for 7 days and 250 mg bid q 12 hours daily). Despite this change, at the third occurrence, upon resolution of toxicity, AZD6738 and/or olaparib should be reduced by the 2nd dose reduction to 120 mg qd for 4 days and 200 mg bid q 12 hours daily. If despite these changes, there is a fourth occurrence of toxicity, the patient should be withdrawn from the treatment. Please note that, for each dose reduction, the investigator may choose to reduce AZD6738 or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step. Refer to Table 5 for specific dose modification guidance regarding non-hematological toxicity.

AD-Table 5: Summary of guidance on the management of non- hematologic toxicity for AZD6738 and olaparib

Toxicity	AZD6738 and olaparib
Any non-hematologic toxicity (CTCAE grade ≥ 3)	1st occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue AZD6738 and olaparib . 2nd occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at 1st reduced dose level for non-hematological toxicity The investigator may choose to reduce AZD6738 or olaparib or both drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step if the toxicity recurs. If symptoms do not recover to ≤CTCAE grade 1, discontinue AZD6738 and olaparib . 3rd occurrence Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at 2nd reduced dose level for non-hematological toxicity The investigator may choose to reduce AZD6738 or olaparib or both

Toxicity	AZD6738 and olaparib
	drugs. If only one drug is dose reduced, the second drug may be reduced as an additional step ir the toxicity recurs. If symptoms do not recover to ≤CTCAE grade 1, discontinue AZD6738 and olaparib. 4th occurrence Off-study

Non-hematologic toxicity management guidelines

Non-hematological CTCAE grade 3 and 4 toxicities observed during the course of the study and attributable to AZD6738 and olaparib will first be managed by interruption of the dose. Repeat dose interruptions are to be allowed as required. The maximum duration of any dose interruption is 28 days. Treatment must be interrupted until the patient recovers completely or the toxicity reverts to NCI CTCAE grade 1 or to the baseline CTCAE grade. If an interruption of longer than 28 days is required, the patient should be withdrawn from the study. Where toxicity recurs following re-treatment with AZD6738 and olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then dose reduction or withdrawal is indicated. Upon appropriate resolution of the toxicity (i.e. to CTCAE grade 1 or to baseline CTCAE grade), the patient should restart treatment with AZD6738 and olaparib but with a dose level reduction (as per Table 5). If toxicity recurs, treatment should be interrupted again and, on resolution, a further dose level reduction made.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Sponsor.

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

AZD6738 and olaparib should be stopped before surgery and re-started after wound has healed following recovery.

No stoppage of AZD6738 and olaparib are required for any biopsy procedures.

AZD6738 and olaparib should be discontinued for a minimum of 7 days before a patient undergoes therapeutic palliative radiation treatment.

Management of nausea and vomiting
Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.
No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines

Additional information for patients
Olaparib should be stopped before surgery and re-started after wound has healed following recovery.

No stoppage of olaparib is required for any biopsy procedures.

Olaparib should be discontinued for a minimum of 7 days before a patient undergoes therapeutic palliative radiation treatment.

Other Toxicities
Olaparib dosing should be discontinued for any severe toxicity that does not respond to treatment.

d. Olaparib Warnings and Precautions

MDS/AML

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 gBRCA 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
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 events have been reported in <1% of patients receiving olaparib. The 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 an abnormal 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.

Pregnancy

Pre-clinical data indicate that olaparib can have adverse effects on embryo-fetal survival and development and pregnancy is an Exclusion Criterion for the clinical studies with Olaparib. If any patient becomes pregnant during a study, olaparib must be discontinued and the patient followed up until birth or termination of pregnancy. The clinical protocol gives details on the requirements to report pregnancy and its outcome. Should pregnancy occur, the physician and patient should discuss the risks of continuing the pregnancy.

Male patients should refrain from fathering a child or donating sperm during a study and for 6 months following the last dose of Olaparib.

Contraception

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 and for 6 months after last dose of study drug(s).
Condom with spermicide and one of the following:

- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- 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
- Normal and low dose combined oral pills+male condom with spermicide
- Hormonal shot or injection (eg, Depo-Provera) + male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system -Mirena®)
- + male condomNorelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
- Intravaginal device+male condom with spermicide (eg, EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

Lactation

Lactation is an Exclusion Criterion within the study protocols for olaparib. It is not known whether olaparib is excreted in human milk.

Pregnancy
All outcomes of pregnancy should be reported to AstraZeneca.

Maternal exposure
If a patient becomes pregnant during the course of the study olaparib should be discontinued immediately.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day** i.e., immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

Paternal exposure
Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 6 months *after the last dose* should be followed up and documented.

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 bid (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply. For other overdoses, reporting should be done within 30 days.

e. Metabolism and Drug Interactions

The use of any natural/herbal products or other "folk 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 eCRF.

Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following strong inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known strong inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, idinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

For patients taking any of the above, the required wash-out period prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following CYP3A4 inducers should be avoided:

- Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitol, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting olaparib are:

- phenobarbitol 5 weeks, and for any of the others, 3 weeks.

After randomization, if the use of any strong inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Other Concomitant Medications

Any medications, other than those listed as excluded therapies, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

Anticoagulant Therapy: Patients who are 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. Subcutaneous heparin is permitted.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF.

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

For further detail, see the olaparib Investigator's Brochure (IB).

AD-1.3.2 AZD6738

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. This compound 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.

Clinical data

At the time of preparation of this amendment, there is one ongoing AstraZeneca sponsored clinical study with AZD6738, study D5330C00004.

Study D5330C00004 is a modular, phase I, 2 part, open-label, multicenter study of AZD6738, administered orally, in combination with cytotoxic chemotherapy regimens or novel anti- cancer 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 Recommended Phase 2 Dose of AZD6738.

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 RP2D of AZD6738 given in combination with olaparib, and assess preliminary efficacy in a subsequent expansion(s) in patients with advanced ATM-deficient (Part B1) and ATM-proficient gastric adenocarcinoma (Part B2) and breast cancer patients with BRCA mutations excluding HER2-positive breast cancer patients (Part B3) and TNBC patients with no known BRCA mutations (Part B4)..

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.

As of 1st June 2017, 36 patients in Module 1, 64 patients in Module 2 and 15 patients in Module 3 of Study D5330C00004 have received treatment with AZD6738. In Module 2, the RP2D has been established and patients with gastric cancer are being recruited to expansions in Parts B1 and B2. Amendment 8, which adds Parts B3 and B4 to the study, has been submitted to the regulatory authorities for approval.

AD-Table 6: Cumulative number of patients exposed to AZD6738 and olaparib in Study

D5330C00004

Data generated from Module 2 has been utilized to evaluate the risks and benefits in the current study which contains the same combination of olaparib and AZD6738.

Cohort	Dose level	Dose frequency	Schedule (28 day cycle)	Key AE observations
1	80mg	BD	Day 1 to Day 21	No AEs > CTCAE G2
2	160mg	BD	Day 1 to Day 21	No AEs > CTCAE G2

AD-Table 7: Module 2 - combination with olaparib

Cohort	AZD6738 QD Dose level	AZD6738 Schedule (28 day cycle)	Dose level Olaparib BD Continuous schedule	Key AE observations
1	60mg	Days 1 to 5 and 15-19	100mg	No AEs > CTCAE G2
2	160mg	Days 1 to 7	100mg	No AEs > CTCAE G1
3	80mg	Days 1 to 7	200mg	No AEs > CTCAE G2
4	160mg	Days 1 to 7	200mg	No AEs > CTCAE G2

AE and Efficacy Summary

Dose-limiting toxicities of AZD6738 and olaparib, observed in the escalation phase included three events of G4 thrombocytopenia associated with bleeding (one each of hematuria, epistaxis, and bleeding from a chest wall tumor) and a prolonged G4 neutropenia. Very common adverse events (≥1/10 according to CIOMS III frequency classification) considered possibly related to AZD6738 and /or olaparib by the investigator include anemia and fatigue. Common adverse events (≥1/100 to < 1/10) include anemia, thrombocytopenia, neutropenia, leucopenia, fatigue, anorexia, nausea and vomiting, diarrhea, dizziness, increased blood creatinine and asthenia. Effects on bone marrow are anticipated in the clinic and may occur in the second or third week of dosing but may also arise after the first cycle resulting in dosing delays. These events are deemed schedule limiting, rather than dose limiting toxicities as the main issue is a delayed recovery of the platelets. Myelosuppression has been successfully managed with dose interruptions, dose reductions (dose and schedule) and supportive measures such as blood transfusions. Hematology and biochemistry blood counts will be monitored each cycle in the clinic and patients will be excluded from clinical studies with AZD6738 if they have significant baseline gastrointestinal pathology.

The combination of Olaparib and AZD6738 has been administered to 64 patients with advanced malignancy with the goal of establishing the dosing schedule. The recommended phase 2 dose was established as 160 mg OD AZD6738 days 1-7 in combination with 300 mg BD olaparib on a 28 day cycle. The dosing schedule of AZD6738 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 IC_{90} threshold (based on ATR enzyme inhibition assay in LoVo cells) and the GI_{90} threshold (based on

the cellular growth inhibition activity in LoVo cells) across the full dosing interval i.e 24 h. Please refer to AZD6738 IB 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 [71], 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.

Potential Benefits

To date, AZD6738 has been administered to approximately 167 subjects (64 in combination with olaparib) as part of AZ sponsored studies or as part of the AZ Externally Sponsored Research program. AZD6738 has shown some clinical activity as monotherapy. Data is presently limited to 24 evaluable subjects from a non-AZ sponsored Phase I dose escalation study in advanced solid tumors (NCT02223923); PRs were observed in 2 patients (8%), one confirmed, a recurrent squamous cell cancer of the oral cavity and a recurrent undifferentiated nasopharyngeal carcinoma, and SD for 6 months or more in observed in 5 patients (21%). (ref AACR study).
AZD6738 in combination with olaparib is considered to have a positive benefit-risk profile for all patients with advanced cancer. In Module 2 of Study D5330C00004, the clinical validity of this approach has been demonstrated with five patients experiencing confirmed RECIST partial responses: two confirmed responses in two patients with BRCA1 mutant triple-negative breast cancer, one confirmed response in a patient with BRCA2 mutant ER+ breast cancer, one confirmed response in a patient with BRCA1 mutated pancreatic cancer and one confirmed response in a patient with BRCA1 mutated pancreatic cancer. In addition, radiological response have been observed in sporadic tumors in combination with radiation (PATRIOT) and in combination with paclitaxel (Pre-VIKTORY).

Potential Risks

As of 1st June 2017, no AZD6738 monotherapy studies have been completed, and AZD6738 has been administered to approximately 49 subjects as monotherapy in Studies D5330C00001, D5330C00004 and D5330C00002). Thrombocytopenia and raised amylase have been reported when AZD6738 has been given as monotherapy and hematological toxicities (thrombocytopenia, neutropenia and anemia) when AZD6738 has been given in combination. Anemia, nausea and fatigue are very common across the program. Overall, such events were predictable from pre-clinical data and from what is known about the mechanism of action of AZD6738 and the combination drug olaparib. The observed toxicities in the clinical setting have been manageable with current practice. None of the events have been fatal.

No reproductive toxicology nor teratogenic studies have been conducted with AZD6738 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breast feeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment.

A number of potential safety signals have been identified on the basis of general toxicology, safety pharmacology, genotoxicity and clinical studies, which were predictable from pre-clinical studies and the mode of action of AZD6738. Most of these signals have not been confirmed to be causally related to AZD6738; some are considered potential risks which are being monitored in ongoing clinical trials e.g. gastrointestinal toxicity, hepatic toxicity. The principal risk associated with the AZD6738 + olaparib combination is exacerbation of hematologic toxicity which is considered an Adverse Drug Reaction or identified risk for the AZD6738. In addition, some clinical

toxicities from AZD6738 overlap with those seen with olaparib use in humans e.g. anemia, neutropenia, leukopenia, thrombocytopenia of potential prolonged duration. While only a small number of patients have been exposed to the combination, a tolerable dose and schedule has been reached. Risk minimization and detailed toxicity management guidelines ae incorporated in the current protocol and the sponsor will continued to monitor the clinical and nonclinical data for emerging safety information. The risks are manageable within current clinical practice with the measures already in place and do not change the benefit / risk profile for AZD6738 in the ongoing and planned clinical studies.

The safety profile of AZD6738 when combined with olaparib has been shown to be acceptable, and AZD6738 has shown activity in several tumor types in the clinical development program to date. Considering the
measures taken to minimize risk to patients participating in the Phase I and II clinical studies, the identified and potential risks associated with AZD6738 in combination with olaparib are justified by the anticipated benefits that may be afforded to patients with advanced cancer.

Please refer to the Investigator's Brochure (IB) for additional information regarding AZD6738.

a. Formulation

Laboratory code: AZD6738, AZ13386215

CAS No.: 1352226-88-0

Molecular formula: C20H24N6O2S

Relative molecular mass: 412.51

b. Dosage, Administration, and Storage

AZD6738 is a crystalline powder. The solubility of AZD6738 free base has been measured as >100 mg/mL in Simulated Gastric Fluid (pH 1.6) and 0.76 mg/mL in Fasted State Simulated Intestinal Fluid (pH 6.5). It has an estimated pKa of 3.7.

The drug product is presented as a range of oral, direct compression, coated tablets containing 20 to 100 mg of AZD6738.

AZD6738 coated tablets contain a blend of AZD6738, mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and silicon dioxide. The coating is Opadry® II white.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all remaining tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g. forgetting to take the tablets or vomiting) or need to modify the timing of a scheduled dose for any reason, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. The dose should not be taken more than 2 hours in advance of the 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. Doses should not be taken fewer than 10 hours apart

Storage
AZD6738 tablets should be stored below 30°C in induction sealed HDPE bottles until use.

The product should be stored in the pack provided and used according to the instructions on the label.

c. Dosage Modification

See Section 1.3.1c above for olaparib + AZD6738 combination dose modification guidelines.

d. AZD6738 Warnings and Precautions

Possible drug interactions
The potential effect of concomitant medication, herbal supplements and/or ingestion of foods that significantly modulate or induce CYP3A4 or Pgp activity are considered in the individual study protocol.

AZD6738 has a low potential to induce CYP1A2, CYP2B6 and CYP3A4 mRNA *in vitro*. Evidence of induction will be monitored for in clinical studies via measurement of 4β-hydroxycholesterol. Guidance on concomitant use of medications that are metabolized by CYP3A4 and have a narrow therapeutic index is provided in individual study protocol.
AZD6738 is an inhibitor of human OATP1B1. Guidance on concomitant use of medications that are OATP1B1 substrates is provided in individual study protocol.

Bone marrow and haematological effects
Thrombocytopenia and anaemia have been reported during clinical use of AZD6738 as monotherapy, and thrombocytopenia, neutropenia and anaemia when AZD6738 is used in combination with myelosuppressive agents (see Section 5.4 for further details). The timing of observed nadirs, especially of platelets when AZD6738 is used in combination with myelosuppressive drugs appears to vary by schedule as well as dose of AZD6738, and remains the subject of investigation in ongoing clinical studies and for at least for some schedules may occur later than might be expected from administration of the myelosuppressive agent alone. Patients starting on AZD6738 therapy should have adequate baseline bone marrow function, as defined in the individual study protocol, with full blood counts monitored closely through study treatment. Any occurrence of clinically significant changes in haematological parameters in a patient will result in interruption of treatment with AZD6738 immediately until all abnormalities return to normal or to their baseline state.

Gastrointestinal effects
Patients will be excluded from clinical studies with AZD6738 if they have significant gastrointestinal symptoms or pathology. The occurrence of GI effects will be monitored for as part of the routine collection of adverse events and patients treated appropriately.

Hepatobiliary effects
Patients starting on AZD6738 therapy should have adequate baseline hepatobiliary function, as defined in the individual study protocol, with liver function tests monitored closely through study treatment. Any occurrence of clinically significant changes in ALT, AST, ALP, INR or other evidence of impairment to the synthesis function of the liver in a patient will result in interruption of treatment with AZD6738 immediately until all abnormalities return to normal or to their baseline state.
Additionally, energy drinks, herbal remedies and food supplements will be restricted.
Patients' laboratory findings will be assessed against the FDA's guidelines (Hy's law) for drug induced liver injury (FDA Guideline 2007).

Cardiovascular effects
Patients will be excluded from clinical studies with AZD6738 if they have significant cardiovascular morbidity. Any occurrence of clinically significant changes in blood pressure will result in interruption of treatment with AZD6738 immediately until all abnormalities return to normal or to their baseline

state.

The results of pharmacokinetic-pharmacodynamic modelling conducted to ascertain the likelihood for effects on blood pressure in the clinic, indicate that clinically significant effects of blood pressure are unlikely at those doses to be explored in this study (see Section 4.2.8.3 for further details).

Reproductive precautions
Conception must be avoided during exposure to AZD6738. Women of childbearing potential and men will be required to agree to use adequate contraception prior to study participation and for an appropriate period thereafter (as described in the clinical study protocol).
Male subjects should abstain from sperm donation during exposure to AZD6738.
Both men and women will be fully informed of the lack of reproductive toxicity testing, and women of child bearing potential must have a negative pregnancy test prior to enrolment.
AstraZeneca should be notified of any pregnancy (including partners of male subjects) that occurs during participation in studies of AZD6738. AZD6738 should not be administered to pregnant or breast-feeding women.

Photosensitising potential
Non-clinical evaluation of AZD6738 for phototoxic potential produced positive *in vitro* but negative *in vivo* findings (4.3.8.1, 4.3.9.9). Two cases of sunburn in patients receiving AZD6738 have been reported. Phototoxicity is not designated an important risk, but AZD6738 is an inhibitor of DNA damage repair it is probably reasonable to advise patients to avoid excessive sun exposure while receiving AZD6738.

e. Metabolism and Drug Interactions

Avoid concomitant medications, herbal supplements and/or ingestion of foods that strongly modulate CYP3A4 activity.

If the Investigator feels that concomitant administration of medications, herbal supplements or foods that strongly modulate CYP3A4 activity is necessary based upon medical judgement, such products may be administered with caution following discussion between the Investigator and the Sponsor.

Concomitant medication may be given as medically indicated with the following exceptions:

- The principal enzyme for metabolizing AZD6738 is CYP3A4. Patients should avoid concomitant drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 activity from the time they enter the screening period until 28 days after the last dose of study medication.
- AZD6738 is a potential inducer of CYP3A4. Caution should be applied with coadministration of drugs that are either completely metabolized by CYP3A4 or that are CYP3A4 substrates and also have a narrow therapeutic index.
- Strong CYP3A4 inducers for patients taking any of these drugs the required wash-out periods prior to starting AZD6738 is 2 weeks, except for St. John's Wort, which is 3 weeks.
- If the use of any strong inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the trials office and a decision to allow the patient to continue in the study will be made on a case-by-case basis. Following the DLT assessment period and if the patient is continuing to receive AZD6738 on the basis of clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria, if the Investigator feels that concomitant administration of medications, herbal supplements or foods that significantly modulate CYP3A4 activity is necessary based upon medical judgement, such products may be administered with caution following discussion between the Investigator and the AZ Study Physician.

AZD6738 is an inhibitor of OATP1B1. Co-administration of substrates of OATP1B1 may affect exposure to AZD6738; therefore, it is recommended that caution should be applied when such drugs are to be administered with AZD6738.

The use of any natural/herbal products or other 'folk remedies' should be discouraged.

AD-1.4 CONCOMITANT AND EXCLUDED THERAPIES

AD-1.4.1 Concomitant Therapy

Refer to the main body of the protocol (Concomitant and Excluded Therapies) for concomitant therapies allowed.

Palliative radiotherapy
Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF. Study treatment should be discontinued for a minimum of 3 days before the patient undergoes palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

AD-1.4.2 Excluded Therapy

The following restrictions apply during the entire duration of study treatment:

- No other investigational therapy should be given to patients.
- No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, herbal therapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial. The patient can receive a stable dose of corticosteroids during the study if these were started at least 4 weeks prior to treatment, as per exclusion criteria. Bisphosphonates and Denosumab for bone metastases are allowed if these were started at least 4 weeks prior to treatment with study drug. Octreotide is allowed if dose is stable for >3 months with no worsening of carcinoid syndrome. Hormonal therapy with luteinizing hormone-releasing hormone (LHRH) analogues for medical castration in patients with castrate-resistant prostate cancer are permitted. Palliative radiotherapy is allowed for pre- existing small areas of painful metastases that cannot be managed with local or systemic analgesics if no evidence of disease progression is present.
- Live virus and bacterial vaccines should not be administered whilst 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 are unknown.
- Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days after the last dose of study medication. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, this restriction is required to ensure patient safety.

AD-1.5 STUDY ASSESSMENTS

	Screening	Day 1 of Cycle 1	Day 1 of each cycle[l]	Every 8 weeks	End of Study	30 Day Follow-up	Long term Follow Up as per main protocol
Visit window (days)	28[i]	+/- 3	+/-	+/- 3	+/- 3	+/- 7	+/- 7
Informed consent	X						
Inclusion/Exclusion Criteria	X						
Pregnancy Test[a]	X	X					
Molecular Selection of Patients based on Archival Tumor Tissue (Paraffin	X						
Medical History	X						
Physical examination, weight and vital signs [b]	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Laboratory tests (Clinical Chemistry/hematology/urinalysis/coagulation)[c]	X	X[h]	X		X[d]		
Concomitant medications	X	X	X		X		
Dosing compliance		X	X		X		
Adverse events	X	X	X	X	X	X	
Echocardiology/MUGA[j]	X						
ECG [k]	X						
RECIST Assessments [e]	X			X	X	X	
Tumor Tissue (Paraffin embedded) (optional)[f]		X			X		
Plasma Sample[g]		X		X	X		
Anti-cancer therapy follow-up							X

a Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. 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.

b A complete physical examination will be performed at the following timepoints (within 24 hours of visit): 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). Vital signs (heart rate, systolic and diastolic blood pressure, oxygen saturation (pulse oximetry), respiration rate, weight, height (at screening) and temperature)

c 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 thromboplastin 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. If APTT testing is not locally available, Partial Thromboplastin Time (PTT) testing may be done along with INR. Any clinically significant results on

PTT will be confirmed with APTT.

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 AstraZeneca Patient Safety for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

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]).

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.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities.

These tests will be performed by the hospital's local laboratory. There is a 48 hr window for performance of lab testing for each visit. 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 G 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

d 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.

e 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. 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).

f Tumor sample at baseline if feasible (optional). The sample can be collected up to 4 weeks before the first dose. Therefore, any sample collected during this time period prior to study enrollment can be used as baseline sample. The tumor sample for use in genetic and protein analyses should be formalin-fixed and embedded in paraffin according to standard procedures at each institution. Additional tumor samples may also be collected and used fresh or frozen.

Tumor sample at progression or discontinuation if feasible (optional). The sample can be collected at progression or discontinuation, or any time between progression and discontinuation from the study. The tumor sample for use in genetic and protein analyses should be formalin-fixed and embedded in paraffin according to standard procedures at each institution. Additional tumor samples may also be collected and used fresh or frozen

g Plasma samples (optional) will be collected at baseline, on treatment and at progression/ discontinuation on study to isolate ctDNA to determine the mutational profile and changes thereof. The plasma sample at baseline can be collected up to 2 weeks before the first dose. Samples on study should be taken at the end of the first cycle (+/- 7 days), and at the end of the cycles 4, 6 and 10 (+/- 7 days) and at progression or discontinuation or any time between progression and discontinuation from the study

Additional samples (optional) after cycle 10 and before progression can be collected, if the investigator deems a particular time point of interest. However, samples should not be collected more frequent than every 2 cycles. F describes the procedures

for collection, processing, storage and shipment of plasma criteria.

h. Results of all cycle 1 day 1 laboratory tests must re-meet eligibility criteria

i: Screening to be performed within 28 days unless otherwise specified

j: Echocardiography will also be carried out if a patient develops signs and/or symptoms suggestive of a deterioration in left ventricular function or in case of the pre-specified ECG finding such as T-wave inversions.

Echocardiography should include assessment of left ventricular end-systolic volume, left ventricular end-diastolic volume and LVEF. If an Echocardiography scan cannot be taken a MUGA scan to assess left ventricular ejection fraction (LVEF) will be conducted. The modality of the cardiac function assessments must be consistent within patient, ie, if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required. The patient should also be examined using the same machine and operator throughout the study wherever possible. Other alternative methods of assessments could be used additionally if they are a part of the local standard of care, or if the investigator considers them necessary for the therapeutic management of the patient. Important cardiac symptoms should be reported as AEs/SAEs and should be carefully evaluated in regard to developing of acute or worsening of chronic cardiac failure, especially in anthracycline treated patients. Congestive cardiac failure should be treated and followed according to standard medical practice.

k: Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. For each time point 3 ECG recordings should be taken one after another. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study.

If an abnormal ECG finding at baseline is considered by the investigator to be clinically significant, it should be reported as a concurrent condition.

l: Continuous use of Olaparib is suitable during this window

APPENDIX E: AZD1775 plus olaparib in patients with either *TP53* or *KRAS* mutations or mutations in both, *TP53* and *KRAS*

This page is intentionally left blank.

APPENDIX F: Collection of plasma, preparation and shipment of ctDNA samples

Plasma should be collected in two 10 mL purple-top EDTA-containing vacutainer tubes and gently turned end over end 3-4 times upon collection to dissolve the EDTA and prevent coagulation. Tubes can then be kept at room temperature, and should be centrifuged at 1000 x g for 10 minutes in a clinical centrifuge within 4 hours of collection (sooner is better). Tubes should be carefully balanced in the centrifuge to avoid vibrations which might disrupt WBCs. The centrifuge should be stopped in "brake off" mode.

Plasma should be dispensed into cryovials in 1mL aliquots, and frozen at -80^{o}C. Care should be taken to avoid the buffy coat by not pipetting the last 5mm of plasma above the buffy coat layer. Once the plasma is frozen, it should not be thawed until it is ready to be processed for sequencing. Samples should be shipped to the following laboratory on dry ice overnight:

As plasma samples are analyzed for mutations in ctDNA in a retrospective manner, samples should be stored at the other sites outside Yale and shipped in batches at a later time to be agreed with the analyzing laboratory.

Samples from participating sites outside of Yale should be shipped to the following laboratory on dry ice overnight:

Attn: Azeet Narayan
Laboratory of Abhijit Patel
Department of Therapeutic Radiology
Yale School of Medicine
15 York Street
Room HRT 213C
New Haven, CT 06510

Appendix G: Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law

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

1. 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

2. 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)

3. 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/A:T 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; 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 H: Acknowledgment of the Investigators

PROTOCOL TITLE: A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination with AZD1775, AZD5363, and AZD6738 in Advanced Solid Tumors- OLAPCO (OLAParib COmbinations)

Version Date: _____

Acknowledgement of the Investigator:

1.) I have read this protocol and agree that the study is ethical

2.) I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines

3.) I agree to maintain the confidentiality of all information received or developed in connection with this protocol

_____ _____
Signature of Investigator: Date:

_____
Name of Investigator (Printed or Typed)

References

1. MacConaill LE. Existing and emerging technologies for tumor genomic profiling. J Clin Oncol 2013; 31: 1815-1824.
2. Tran B, Dancey JE, Kamel-Reid S et al. Cancer genomics: technology, discovery, and translation. J Clin Oncol 2012; 30: 647-660.
3. Mladenov E, Magin S, Soni A, Iliakis G. DNA double-strand break repair as determinant of cellular radiosensitivity to killing and target in radiation therapy. Front Oncol 2013; 3: 113.
4. Salk JJ, Fox EJ, Loeb LA. Mutational heterogeneity in human cancers: origin and consequences. Annu Rev Pathol 2010; 5: 51-75.
5. Strom CE, Johansson F, Uhlen M et al. Poly (ADP-ribose) polymerase (PARP) is not involved in base excision repair but PARP inhibition traps a single-strand intermediate. Nucleic Acids Res 2011; 39: 3166-3175.145
6. Bryant HE, Schultz N, Thomas HD et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005; 434: 913-917.
7. Farmer H, McCabe N, Lord CJ et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434: 917-921.
8. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014; 15: 852-861.
9. Fong PC, Yap TA, Boss DS et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010; 28: 2512-2519.
10. Sulkowski PL, Corso CD, Robinson ND, Scanlon SE, Purshouse KR, Bai H, Liu Y, Sundaram RK, Hegan DC, Fons NR, Breuer GA, Song Y, Mishra-Gorur K, De Feyter HM, de Graaf RA, Surovtseva YV, Kachman M, Halene S, Günel M, Glazer PM, Bindra RS. 2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity, Sci Transl Med. 2017 Feb 1;9(375)
10 O'Connor MJ, Martin NM, Smith GC. Targeted cancer therapies based on the inhibition of DNA strand break repair. Oncogene 2007; 26: 7816-7824.
11 Lindsley CW. The Akt/PKB family of protein kinases: a review of small molecule inhibitors and progress towards target validation: a 2009 update. Curr Top Med Chem 2010; 10: 458-477.
12 Altomare DA, Testa JR. Perturbations of the AKT signaling pathway in human cancer. Oncogene 2005; 24: 7455-7464.
13 Michalarea V, Roda D, Drew Y, Carreira S, O'Carrigan BS, Shaw H, Roux R, Kumar S, Ward S, Parmar M, Turner A,Hall E, Fandos SS, Perez R, Tunariu N, Raynaud F, Cullberg M, Foxley A, Lindemann JPO, Pass M, Rugman P, Lopez JS, Banerji U, Basu B, Plummer R, Kristeleit R, de Bono JS, YapTA. Phase I trial combining the PARP inhibitor olaparib (Ola) and AKT inhibitor AZD5363 (AZD) in germline (g)BRCA and non-BRCA mutant (m) advanced cancer patients (pts) incorporating noninvasive monitoring

of cancer mutations Cancer Res Jul 2016, 76 (14 Supplement, abstract CT010); **DOI:** 10.1158/1538-7445

15 Coleman TR, Dunphy WG. Cdc2 regulatory factors. Curr Opin Cell Biol 1994; 6: 877-882.

16 Sherr CJ. Cancer cell cycles. Science 1996; 274: 1672-1677.

17 Wang Y, Li J, Booher RN et al. Radiosensitization of p53 mutant cells by PD0166285, a novel G(2) checkpoint abrogator. Cancer Res 2001; 61: 8211-8217.

18 Do KT WD, Balasubramanian P, Zlott J, Jeong W, Lawrence SM, Kinders RJ, Collins J, Chen AP, Doroshow JH, Kummar S. Phase I trial of AZD1775 (MK1775), a wee1 kinase inhibitor, in patients with refractory solid tumors. J Clin Oncol 2014; 32:5s: abstr 2503.

19 Stankovic T, Stewart GS, Byrd P, Fegan C, Moss PA, Taylor AM. ATM mutations in sporadic lymphoid tumours. Leuk Lymphoma. 2002 Aug;43(8):1563-71

20 Grønbæk K, Worm J, Ralfkiaer E, Ahrenkiel V, Hokland P and Guldberg P. ATM mutations are associated with inactivation of the ARF-TP53 tumor suppressor pathway in diffuse large B-cell lymphoma. Blood 2002;100 (4):1430-1437.

21 Ambatipudi S, Gerstung M, Gowda R, Pai P, Borges AM, Schäffer AA, Beerenwinkel N, Mahimkar MB. Genomic profiling of advanced-stage oral cancers reveals chromosome 11q alterations as markers of poor clinical outcome. PLoS One. 2011 6(2):e17250.

22 Bolt J, Vo QN, Kim WJ, McWhorter AJ, Thomson J, Hagensee ME, Friedlander P, Brown KD, Gilbert J. The ATM/p53 pathway is commonly targeted for inactivation in squamous cell carcinoma of the head and neck (SCCHN) by multiple molecular mechanisms. Oral Oncol. 2005; 41: 1013-20.

23 Mazumder Indra D, Mitra S, Roy A, Mondal RK, Basu PS, Roychoudhury S, Chakravarty R, Panda CK. Alterations of ATM and CADM1 in chromosomal 11q22.3-23.2 region are associated with the development of invasive cervical carcinoma. Hum Genet. 2011; 130(6):735-48.

24 Grabsch H, Dattani M, Barker L, Maughan N, Maude K, Hansen O, Gabbert HE, Quirke P, Mueller W. Expression of DNA double-strand break repair proteins ATM and BRCA1 predicts survival in colorectal cancer. Clin Cancer Res. 2006; 12(5):1494-500.

25 Mukhopadhyay UK, Senderowicz AM, and Ferbeyre G. RNA silencing of checkpoint regulators sensitizes p53-defective prostate cancer cells to chemotherapy while sparing normal cells. Cancer Res. 2005; 65: 2872–2881.

26 Pan Y, Ren KH, He HW, and Shao, RG. Knockdown of Chk1 sensitizes human colon carcinoma HCT116 cells in a p53-dependent manner to lidamycin through abrogation of a G2/M checkpoint and induction of apoptosis. Cancer Biol. Ther. 2009; 8:1559–1566.

27 Powell, SN, DeFrank JS, Connell P, Eogan M, Preffer F, Dombkowski, D, et al. Differential sensitivity of p53(-) and p53(+) cells to caffeine-induced radiosensitization and override of G2 delay. Cancer Res. 1995; 55: 1643–1648.

28 Strunz AM, Peschke P, Waldeck W, Ehemann V, Kissel M, and Debus J. Preferential radiosensitization in p53-mutated human tumour cell lines by pentoxifylline-mediated disruption of the G2/M checkpoint control. Int. J. Radiat. Biol. 2002, 78, 721–732.

29 Tao Y, Leteur C, Zhang P, Castedo M, Pierré A, Golsteyn, RM, et al. Radiosensitization by Chir-124, a selective CHK1 inhibitor: Effects of p53 and cell cycle checkpoints. Cell Cycle 2009, 8, 1196–1205.

30 Parikh RA, White JS, Huang X, Schoppy DW, Baysal BE, Baskaran R, Bakkenist CJ, Saunders WS, Hsu LC, Romkes M, Gollin SM. Loss of distal 11q is associated with DNA repair deficiency and reduced sensitivity to ionizing radiation in head and neck squamous cell carcinoma. Genes Chromosomes Cancer. 2007; 46: 761-75.

31 Tucker CL, Fields S. Lethal combinations. Nat Genet. 2003 Nov;35(3):204-5.

32 Burhans WC and Weinberger M. DNA replication stress, genome instability and aging. Nucleic Acids Research 2007;35(22): 7545–7556

33 Molinari M. Cell cycle checkpoints and their inactivation in human cancer. Cell Prolif 2000; 33: 261-274.

34 Kawabe T. G2 checkpoint abrogators as anticancer drugs. Mol Cancer Ther 2004; 3: 513-519.

35 Bucher N, Britten CD. G2 checkpoint abrogation and checkpoint kinase-1 targeting in the treatment of cancer. Br J Cancer 2008; 98: 523-528.

36 Hirai H, Arai T, Okada M et al. MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer Biol Ther 2010; 9: 514-522.

37 Hirai H, Iwasawa Y, Okada M et al. Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther 2009; 8: 2992-3000.

38 Bridges KA, Hirai H, Buser CA et al. MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells. Clin Cancer Res 2011; 17: 5638-5648.

39 Krajewska M, Heijink AM, Bisselink YJ et al. Forced activation of Cdk1 via wee1 inhibition impairs homologous recombination. Oncogene 2013; 32: 3001-3008.

40 Grabocka E, Pylayeva-Gupta Y, Jones MJ et al. Wild-type H- and N-Ras promote mutant K-Ras-driven tumorigenesis by modulating the DNA damage response. Cancer Cell 2014; 25: 243-256.

41 Dupont Jensen J, Laenkholm AV, Knoop A et al. PIK3CA mutations may be discordant between primary and corresponding metastatic disease in breast cancer. Clin Cancer Res 2011; 17: 667-677.

42 Shen Y, Rehman FL, Feng Y et al. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. Clin Cancer Res 2013; 19: 5003-5015.

43 Forster MD, Dedes KJ, Sandhu S et al. Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer. Nat Rev Clin Oncol 2011; 8: 302-306.

44 Ibrahim YH, Garcia-Garcia C, Serra V et al. PI3K inhibition impairs BRCA1/2 expression and sensitizes BRCA-proficient triple-negative breast cancer to PARP inhibition. Cancer Discov 2012; 2: 1036-1047.

45 Juvekar A, Burga LN, Hu H et al. Combining a PI3K inhibitor with a PARP inhibitor provides an

effective therapy for BRCA1-related breast cancer. Cancer Discov 2012; 2: 1048-1063.

46 Matulonis U WG, Birrer MJ, Neville Westin S, Quy P, Bell-McGuinn KM, Lasonde B, Whalen C, Aghajanian C, Solit DB, Mills GB, Cantley L, Winer EP. Phase I study of oral BKM120 and oral olaparib for high-grade serous ovarian cancer (HGSC) or triple-negative breast cancer (TNBC). J Clin Oncol 2014; 32:5s,: abstr 2510.

47 Wiegand, Kimberly C, Bryan T Hennessy, et. al. A functional proteogenomic analysis of endometrioid and clear cell carcinomas using reverse phase protein array and mutation analysis: protein expression is histotype-specific and loss of *ARID1A/*BAF250a is associated with AKT phosphorylation. BMC Cancer 2014; 14(120).

48 Samartzis, Eleftherios P., Katrin Gutsche, et al. Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition. Oncoterget 2014; 5(14).

49 Wu, Jennifer N. and Charles W.M. Roberts *ARID1A* mutations in Cancer: Another Epigenetic Tumor Suppressor? Cancer Discovery 2013; 35-43.

50 Davies BR, Greenwood H, Dudley P et al. Preclinical pharmacology of AZD5363, an inhibitor of AKT: pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. Mol Cancer Ther 2012; 11: 873-887.

51 Janku F, Wheler JJ, Naing A et al. PIK3CA mutation H1047R is associated with response to PI3K/AKT/mTOR signaling pathway inhibitors in early-phase clinical trials. Cancer Res 2013; 73: 276-284.

52 Polivka J, Jr., Janku F. Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway. Pharmacol Ther 2014; 142: 164-175.

53 Stephens PJ, Tarpey PS, Davies H et al. The landscape of cancer genes and mutational processes in breast cancer. Nature 2012; 486: 400-404.

54 Banerji S, Cibulskis K, Rangel-Escareno C et al. Sequence analysis of mutations and translocations across breast cancer subtypes. Nature 2012; 486: 405-409.

55 Willner J, Wurz K, Allison KH et al. Alternate molecular genetic pathways in ovarian carcinomas of common histological types. Hum Pathol 2007; 38: 607-613.

56 Cheung LW, Hennessy BT, Li J et al. High frequency of PIK3R1 and PIK3R2 mutations in endometrial cancer elucidates a novel mechanism for regulation of PTEN protein stability. Cancer Discov 2011; 1: 170-185.

57 Carpten JD, Faber AL, Horn C et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. Nature 2007; 448: 439-444.

58 Bleeker FE, Felicioni L, Buttitta F et al. AKT1(E17K) in human solid tumours. Oncogene 2008; 27: 5648-5650.

59 Cohen Y, Shalmon B, Korach J et al. AKT1 pleckstrin homology domain E17K activating mutation in endometrial carcinoma. Gynecol Oncol 2010; 116: 88-91.

60 Shoji K, Oda K, Nakagawa S et al. The oncogenic mutation in the pleckstrin homology domain of AKT1 in endometrial carcinomas. Br J Cancer 2009; 101: 145-148.

61 Do H, Salemi R, Murone C et al. Rarity of AKT1 and AKT3 E17K mutations in squamous cell carcinoma of lung. Cell Cycle 2010; 9: 4411-4412.

62 Malanga D, Scrima M, De Marco C et al. Activating E17K mutation in the gene encoding the protein kinase AKT1 in a subset of squamous cell carcinoma of the lung. Cell Cycle 2008; 7: 665-669.

63 Do H, Solomon B, Mitchell PL et al. Detection of the transforming AKT1 mutation E17K in non-small cell lung cancer by high resolution melting. BMC Res Notes 2008; 1: 14.

64 Kim MS, Jeong EG, Yoo NJ, Lee SH. Mutational analysis of oncogenic AKT E17K mutation in common solid cancers and acute leukaemias. Br J Cancer 2008; 98: 1533-1535.

65 Soung YH, Lee JW, Nam SW et al. Mutational analysis of AKT1, AKT2 and AKT3 genes in common human carcinomas. Oncology 2006; 70: 285-289.

66 Parikh C, Janakiraman V, Wu WI et al. Disruption of PH-kinase domain interactions leads to oncogenic activation of AKT in human cancers. Proc Natl Acad Sci U S A 2012; 109: 19368-19373.

67 Davies MA, Stemke-Hale K, Tellez C et al. A novel AKT3 mutation in melanoma tumours and cell lines. Br J Cancer 2008; 99: 1265-1268.

68 Dutt A, Salvesen HGB, Greulich H et al. Somatic mutations are present in all members of the AKT family in endometrial carcinoma. Br J Cancer 2009; 101: 1218-1219; author reply 1220-1211

69 Curtin N. DNA repair dysregulation from cancer driver to therapeutic target. Nature Reviews - Cancer 2012; 12: 801-817.

70 Kim H, George E, Ragland RL, Rafail S, Zhang R, Krepler C, Morgan M, Herlyn M, Brown EJ, Simpkins F. Targeting the ATR/CHK1 axis with PARP inhibition results in tumor regression in BRCA mutant ovarian cancer models. Clin Cancer Res. 2016 Dec 19. pii: c

71 Bauer M, Goldstein M, christmann M, Becker H, Heylmann D, Kaina B. Human monocytes are severely impaired in base and DNA double-strand break repair that renders them vulnerable to oxidative stress. Proc Natl Acad Sci USA. 2011 Dec 27;108(52): 21105-21110.