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Combination ATR and PARP Inhibitor (CAPRI) trial with AZD6738 and olaparib in recurrent ovarian cancer

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Medical Director: [redacted]

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Table of Contents

PRINCIPAL INVESTIGATOR SIGNATURE 6
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 7
1. STUDY SUMMARY 8
1.1 Synopsis 8
2 INTRODUCTION 9
2.1 Background 9
2.2 Pre-clinical experience 11
2.3 Toxicology and safety pharmacology summary 23
2.4 Clinical experience 25
2.5 Research hypothesis 28
2.6 Rationale for conducting this study 28
2.7 Benefit/risk and ethical assessment 28
3.1 Primary objectives 29
3.2 Secondary objectives 29
3.3 Exploratory objectives 29
4 STUDY PLAN AND PROCEDURES 30
4.1 Overall study design and flow chart 30
4.2 Rationale for study design, doses and control groups 49
4.3 End of Study Definition 49
5 PATIENT SELECTION CRITERIA 49
5.1 Inclusion criteria 49
5.2 Exclusion criteria 51
6 STUDY CONDUCT 53
6.1 Restrictions during the study 53
6.1.1 Anti-cancer therapy 53
6.1.2 Herbal supplements 53
6.1.3 Exposure to sunlight 53
6.1.4 Grapefruit juice 53
6.2 Subject enrollment, randomization, and initiation of investigational product 53
6.3 Procedures for handling subjects incorrectly enrolled or initiated on investigational product 54
6.4 Blinding and procedures for unblinding the study 54
6.4.1 Methods for ensuring blinding 54
6.4.2 Methods for unblinding the study 54
6.5 Treatments 54
6.5.1 Identity of investigational product(s) 54
6.5.2 Doses and treatment regimens 55
6.5.3 Labeling 56
6.5.4 Storage 56
6.5.5 Management of toxicity 56

Confidential and Proprietary Information of the University of Pennsylvania

6.5.6 Interruptions for intercurrent non-toxicity related events 73
6.6 Concomitant and post-study treatment(s) 74
6.6.1 Medications that may NOT be administered 74
6.6.2 Restricted concomitant medications 74
6.7 Treatment compliance 76
6.7.1 Accountability 76
6.8 Discontinuation of investigational product 77
6.8.1 Procedures for discontinuation of a subject from investigational product (End of treatment) 77
6.9 Withdrawal from study 77
7 COLLECTION OF STUDY VARIABLES 78
7.1 Recording of data 78
7.2 Data collection at enrollment and follow-up 78
7.3 Enrollment procedures 78
7.4 Study procedures 79
7.5 Follow-up procedures 80
7.6 Efficacy 80
7.7 Safety: Adverse Events and Serious Adverse Events 81
7.7.1 Definition of Adverse Events (AE) 81
7.7.2 Definition of Serious Adverse Events (SAE) 82
7.7.3 Classification of an Adverse Event 83
7.7.4 Time Period and Frequency for Event Assessment and Follow-Up 84
7.7.5 Events of Special Interest 85
7.7.6 Adverse Event Reporting 85
7.7.7 Serious Adverse Event Reporting 86
7.7.8 Laboratory safety assessment 88
7.8 Physical examination 89
7.8.1 EKG 89
7.8.2 Vital signs 89
7.8.3 Bone marrow or blood cytogenetic analysis 89
7.8.4 Volume of blood 89
7.9 Handling, storage and destruction of biological samples 90
7.9.1 Labeling and shipment of biohazard samples 90
7.9.2 Chain of custody of biological samples 90
7.10 Withdrawal of informed consent for donated biological samples 91
8 ETHICAL AND REGULATORY REQUIREMENTS 91
8.1 Ethical conduct of the study 91
8.2 Subject data protection 91
8.3 Ethics and regulatory review 91
8.4 Exceptions and Deviations 91
8.5 Informed consent 91
8.6 Changes to the protocol and informed consent form 92
8.7 Audits and inspections 92
9 STUDY MANAGEMENT 92
9.1 Training of study site personnel 92

Confidential and Proprietary Information of the University of Pennsylvania

9.2 Monitoring of the study....92
9.2.1 Source data....92
9.3 Study timetable and end of study....92
10 DATA MANAGEMENT....92
11 EVALUATION AND CALCULATION OF VARIABLES....92
11.1 Calculation or derivation of efficacy variable(s)....92
11.2 Calculation or derivation of safety variable(s)....93
12 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION....93
12.1 Description of analysis sets....93
12.1.1 Efficacy analysis set....93
12.1.2 Safety analysis set....93
12.2 Methods of statistical analyses....93
12.2.1 Interim analyses....94
12.3 Determination of sample size....94
12.4 Data monitoring committee....96
12.5 Overdose....96
13 LIST OF REFERENCES....97
14 Appendix A. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law....100
15 Appendix B. Subject Dosing Diary....105
16 Appendix C. Medication Instructions - Cohorts A, B, C....121
17 Appendix D. Medication Instructions - Cohort D....123
18 Appendix E. CYP3A Inhibitors and Inducers....125
19 Appendix F. Safety Review Committee....126
19.1 Safety Review Committee Members Details....127
19.2 Draft Agenda for Safety Review Meetings....128
19.3 Safety Review Committee Minutes Template....129
19.4 CAPRI Cohort D Safety Review Committee Meeting Dosing discussion and Approval....130
19.5 Additional data requirements for AZD6738 SRC/medical review....131

Table of Tables

Table 1. Summary of key efficacy variable in studies D0810C00002, D0810C00009, D0810C00020, D0810C00024 (ovarian cancer)....25
Table 2. Dose Cohorts explored in AstraZeneca Study 4 (D5330C00004)....32
Table 3. Indicative dose levels to explore in Cohort D Dose and Schedule Finding Part I....33
Table 4. Dose escalation or de-escalation for the proposed BOIN design....36
Table 5. Study Schedule Cohorts A, B, and C....43
Table 6. Study Schedule Cohort D....46

Confidential and Proprietary Information of the University of Pennsylvania

Table 7. Guidance for dose reductions for AZD6738 for hematological toxicity 57
Table 8. Guidance for dose reductions for Olaparib for hematological toxicity 58
Table 9. Anemia only 59
Table 10. Neutropenia and/or leukopenia only 61
Table 11. Thrombocytopenia only 62
Table 12. Guidance for dose reductions for AZD6738 for non-hematological toxicity 67
Table 13. Guidance for dose reductions of Olaparib for non-hematological toxicity 68
Table 14. Guidance on the management of Grade ≥ 3 non-hematologic toxicities for AZD6783 and olaparib 69
Table 15. Volume of blood to be drawn from each subject 89

Table of Figures

Figure 1. Concept of Synthetic Lethality 9
Figure 2. Graphical plot of olaparib sensitive cell lines (IC 50 <uM) arranged by known BRCA 1 / 2 mutation or low expression with HRR genes 11
Figure 3. HBCX-10 tumor response to different continuous doses of olaparib 12
Figure 4. Steady state simulation: relationship between PARP and DNA SSBs 13
Figure 5. Protein expression of ATR/CHK1 signaling pathway with ATR inhibition in LoVo cells 15
Figure 6. Diagram illustrating hypothesis for synergy with combination PARPi and ATRi 17
Figure 7. Fold shift in GI50 of olaparib with AZD6738 across panel of 26 gastric cell lines in vitro 18
Figure 8. Incucyte live cell in vitro growth inhibition time course assays for AZD6738 and olaparib in ATM-deficient NCI-H23 lung cancer cell line in vitro 19
Figure 9. Anti-tumor inhibition of HBCx-9 breast cancer primary tumor xenograft model for AZD6738 used in combination with olaparib 19
Figure 10. PARPi alone at the MTD (100mg/kg/day X 7 days) for prolonged treatment results in tumor suppression not regression in a BRCA2 mutant HGSCP PDX (WO-2) 20
Figure 11. PARPi treatment increases ATR signaling and synergizes with ATRi in BRCAMUT, PARPi R, and CCNE1HIGH HGSOC cells and PDX tumors 21
Figure 12. PARPi-ATRi combination increases chromosomal DSBs leading to apoptosis 22
Figure 13. PARPi-ATRi causes tumor regression and extends disease-free interval in platinum - resistant CCNEHIGH PDX, but resistance ultimately results Tumor from patient with recurrent, platinum- resistant HGSOC with *CCNE1* amplification used to develop PDX. Once PDX tumors reached 70-100 mm^3, mice randomized to vehicle, PARPi (50 mg/kg/day, ATRi (AZD6738 50 mg/kg/day) each Day1-5 and PAPRi-ATRi (same doses). Three mice/grp. PDX tumors were measured by sonogram. 23
Figure 14. Cohort D Flow Chart 34
Figure 15. BOIN flow chart 36
Figure 16. Graph of dose limiting toxicity curves 94

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PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	University of Pennsylvania
STUDY TITLE:	Combination ATR and PARP Inhibitor (CAPRI) trial with AZD6738 and olaparib in recurrent ovarian cancer
STUDY ID	[redacted]
PROTOCOL VERSION	Version 18

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name _____ Signature _____

Affiliation: _____ Date _____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
AESI	Adverse events special interest
AML	Acute myelocytic leukemia
ATR	Ataxia telangiectasia and Rad3-related protein
BID	Twice daily
BRCP	Breast cancer resistance protein
CHK	Checkpoint kinases
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DDR	DNA damage response
DSB	DNA double strand breaks
FDA	Food and Drug Administration
HR	Homologous recombination
HRD	Homologous recombination deficiencies
HRR	Homologous recombination deoxyribonucleic acid repair
INR	International normalized ratio
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDR1	Multidrug resistance protein 1
MDS	Myelodysplastic syndrome
MTD	Maximum tolerated dose
NCIOR	National cancer instituteObjective response rate
R	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization
PARP	Pharmacodynamics
PD	Progression free survival
PFS	Phosphatidylinositol 3-kinase-related kinase
PIKK	Pharmacokinetics
PK	Partial response
PR	Red blood cells
RBC	Serious adverse events
SAE	Single strand breaks
SSB	Upper limit of normal
ULN	United States
US	

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1. STUDY SUMMARY

1.1 Synopsis

Title:	Combination ATR and PARP Inhibitor (CAPRI) trial with AZD6738 and olaparib in recurrent ovarian cancer
Short Title:	CAPRI
Study Hypothesis:	The therapeutic inhibition of ATR and PARP will clinically benefit subsets of patients with recurrent ovarian cancer. We hypothesize that combination PARP inhibition with ATR inhibition will be more effective in recurrent platinum sensitive and resistant ovarian cancer than traditional responses to olaparib monotherapy. In addition, we propose that this combination will demonstrate activity in PARP inhibitor resistant ovarian cancer.
Objectives:	1. To determine the safety and tolerability of combination AZD6738 and olaparib in recurrent ovarian cancer patients using Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) for all Cohorts (e.g. Cohorts A, B, C, and D). 2. To determine the objective response rate (CR+PR) of the combination of AZD6738 and olaparib in women with recurrent ovarian cancer in platinum-sensitive and resistant, and PARP inhibitor resistant cohorts (e.g. Cohorts A, B, C, and D). 3. To determine the maximum tolerated dose (MTD) and response rate of an alternative dose and schedule of this combination using a higher dose of AZD6738 and a lower dose of olaparib (in Cohort D) than that tested in Cohorts A to C.
Phase:	I AND II
Enrolling Participants:	Women with recurrent ovarian cancer
Participating Sites:	University of Pennsylvania, Johns Hopkins University, and Harvard University

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2 INTRODUCTION

2.1 Background

Olaparib

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 (Investigator's Brochure, current version). The capsule formulation of olaparib was approved by the United States (US) Food and Drug Administration (FDA) in December 2014 as a monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. In August 2017, the FDA approved olaparib tablets for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.

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 through homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates.

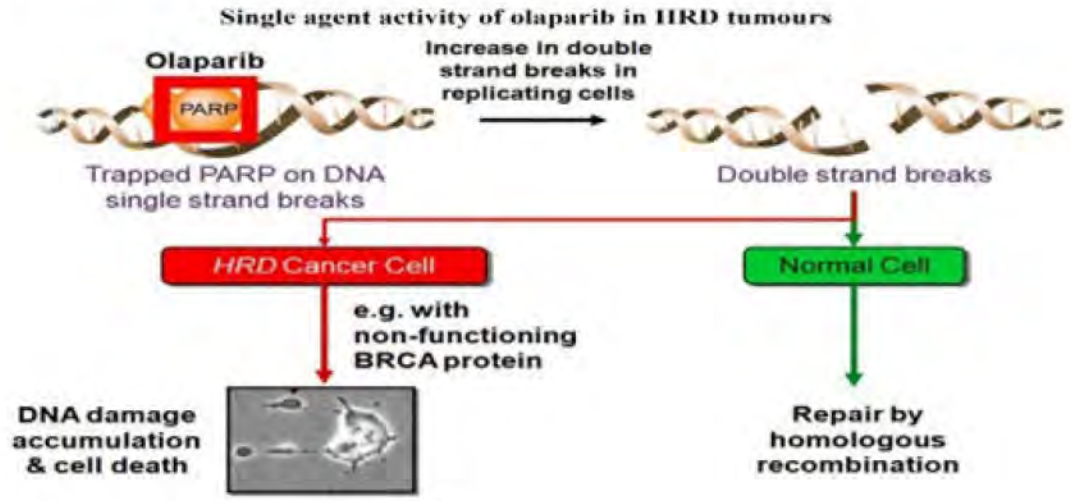


Figure 1. Concept of Synthetic Lethality

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors (PARPi), both in tumor models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011; Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally

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be repaired by HR repair. In the setting of BRCA1 and BRCA2 defective tumors, the DNA DSBs are not repaired leading to cell death. 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 knockout models, either as a stand-alone treatment or in combination with established chemotherapies.

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 both as a single agent and in combination with chemotherapy, ionizing radiation, and other anti-cancer drugs, such as PARPi. DNA-repair inhibitor strategies have been directed to specific targets or pathways for which there is a reason to suppose that selectivity for tumor over normal tissue can be achieved. As a result, most emphasis to date has been placed on a relatively small number of targets such as the poly (ADP-ribose) polymerase 1 (PARP1) and checkpoint kinases (Chk). ATR is an atypical kinase in one of the DNA-damage induced checkpoint pathways that responds to a wide range of DNA damage and replication abnormalities.

During normal DNA replication, ATR is recruited to stalled replication forks where it 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) occurs. 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.

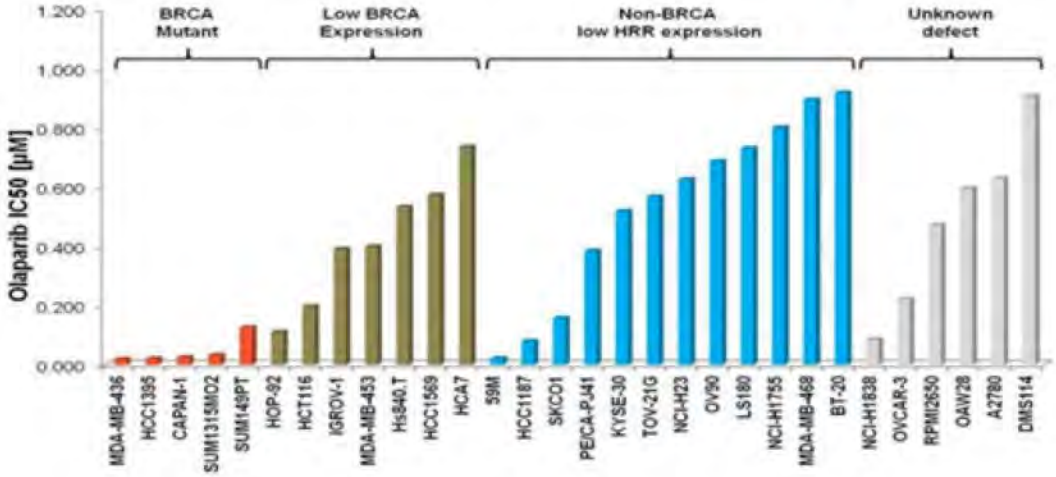
There are multiple molecular features that could be envisaged to affect clinical response to ATR inhibition, and these would include: ATM deficiency, defects in G1/S checkpoint control and (ATR-dependent) replicative stress. The ATR-Chk1 checkpoint pathway serves to ensure cell survival after replication 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.

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2.2 Pre-clinical experience

Olaparib

Graphical plot of olaparib sensitive cell lines (IC_{50} <μM) arranged by known BRCA1/2 mutation status or low expression of HRR genes



Plot of highly olaparib sensitive cell lines (IC_{50}<1 μM) clustered by the presence known deleterious BRCA1/2 mutations (*BRCA* mutant), low BRCA1/2 expression (low BRCA expression), low expression of 1or more HRR genes in the absence of BRCA1/2 mutation/low expression (non-BRCA, low HRR expression) or those without any of these defects (unknown defect).

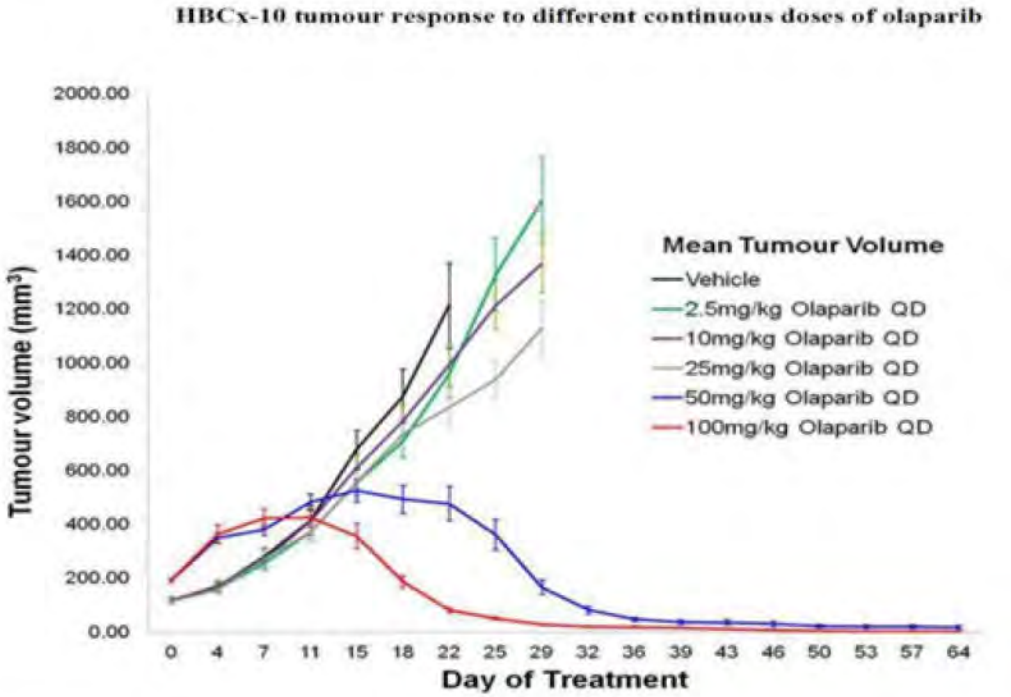
Figure 2. Graphical plot of olaparib sensitive cell lines (IC 50 <uM) arranged by known BRCA 1 / 2 mutation or low expression with HRR genes

Olaparib has been tested across a mixed tumor panel of 95 cancer cells lines, which included ovarian cancer cell lines (Figure 2; Investigator's Brochure, current version). IC_{50} data were calculated and a wide range was found from 18nM to in excess of 10 μM. The panel was also profiled for relative protein and messenger ribonucleic acid gene expression levels of key DNA damage response (DDR) and homologous recombination deoxyribonucleic acid repair (HRR) associated genes such as BRCA1, BRCA2, ATM, ATR, mediator of DNA damage checkpoint protein 1 and MRE11A. Cell lines were classified according to HRD. Enhanced olaparib sensitivity (IC_{50} <1 μM) was observed in cell lines with known BRCA1 or BRCA2 mutations or low expression of HRR genes/proteins. The effective concentration for inhibiting cellular PARP activity in cancer cells by >90% is approximately 30nM to 100nM olaparib in several tumor cell lines, with appropriate DNA SSB-inducing chemotoxic agent (MMS) was also seen in vitro at 100nM maximal PARP-1 inhibition at 100nM. Consistent with this, maximal potentiation which equates to 43.4ng/mL.

To build a preclinical PK/PD/efficacy relationship model, an olaparib sensitive PDX model (HBCx-10) has been used (Figure 3; Investigator's Brochure, current version). This model is derived from a triple negative breast cancer patient who carries a homozygous BRCA2 mutation and who demonstrated response to single agent olaparib. A number of continuous doses were tested in the HBCx-10 PDX model ranging from 2.5mg/kg to 100mg/kg. For doses beneath 50mg/kg no

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tumor regression was seen by Day 30. For the 50mg/kg dose, the time taken to cause tumor regression was extended to 28 days from 17days. Both tumor PD (PAR inhibition) and plasma PK were determined 1 hour after dosing on Days 7 and 14 of continuous dosing.



Mice bearing HBCx-10 tumours (TNBC BRCA2 mutant) were treated when reaching between 100 mm^3 or 200 mm^3 in volume with continuous once daily dosing of olaparib at doses of 2.5, 10, 25, 50 or 100 mg/kg. N=10 tumour-bearing mice for each group. Mice were not dosed beyond Day 30 where no tumour regression was observed. For the 50 mg/kg and 100 mg/kg doses where tumour regression was seen dosing was continued for at least 64 days.
QD Once daily dosing.

Figure 3. HBCX-10 tumor response to different continuous doses of olaparib

There was a clear correlation between dose of olaparib, free levels of olaparib in the plasma and the level of PAR inhibition in the tumor. This information has been used to determine the predicted time above both the tumor PAR IC_{50} and IC_{90} for each of the doses. These data suggest that in the preclinical model either the IC_{50} (56.5nM for tumor PAR) needs to be exceeded for 13 hours or the IC_{90} (382 nM for tumor PAR) for 6 hours. Mechanistic modeling has been used to gain insight into the relationship between tumor PD as measured by PAR concentration reduction and the resulting efficacy as measured by tumor growth inhibition. The results suggest that there is an inverse relationship between PAR and SSB (Figure 4; Investigator's brochure, current version). However, importantly, there are only significant increases in SSB when PAR is reduced by more than 90%. Therefore, only when 90% of PAR levels are inhibited will SSB increase to an extent that will translate into tumor cell death in cells lacking HRR. Furthermore, the clinical activity appears to be associated to high unbound steady states of the drug.

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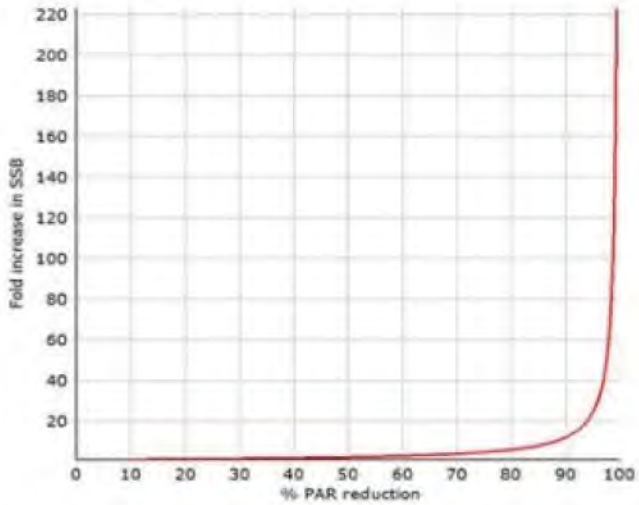


Figure 4. Steady state simulation: relationship between PARP and DNA SSBs

In animal models, bioavailability ranges from 20% (rats) to 80% (dogs) with rapid absorption across the board. Exposure by dose, change in PK with multiple dosing, and plasma protein binding varied by species. Gender differences were only seen in rats. In vitro CYP3A4 and CYP3A5 were show to be the major isoenzymes responsible for metabolism of olaparib. CYP3A was directly inhibited by olaparib, as well as time dependent inhibitor of CYP3A. In vitro studies showed that olaparib was not a substrate for OATP1B1, OATP1B3, or OCT1 hepatic uptake transporters. Olaparib was a substrate for the efflux transporter multi- drug resistance protein 1 (MDR1) Pgp, but not for breast cancer resistance protein (BRCP) or multidrug resistance protein 2 (MRP-2) efflux transporters. Olaparib was an inhibitor of OATp1B1, OCT1, MDR1, weekly BCRP, OCT2, OAT3, MATE1, and MATE2K. Olaparib was not an inhibitor of OATP1B3, MRP-2, or OAT1. Drug material was excreted in the feces.

The nonclinical safety data is taken from repeat dose toxicology studies in rats and dogs, reproductive toxicology in rats and in vitro and in vivo assessment of genotoxic potential. When repeat doses were given for up to six months, the primary toxicity was bone marrow related. All changes showed full or partial recovery following withdrawal of olaparib. In rats, repeated oral daily dosing for 1 to 6 months resulted in reductions in body weight gain, food consumption, red blood cell parameters, white blood cell, neutrophil and/or lymphocyte counts, and changes in reticulocyte and platelet counts, were also seen. These changes were associated with increases in the erythropoietic and/or myelopoietic cell populations within the bone marrow, and with increase in splenic hemopoiesis, hepatocyte pigmentation and/or thymic atrophy. In dogs, decreases in red and white blood cells and platelets were seen and were associated with bone marrow atrophy and with an increase in the myeloid/erythroid (M:E) ratio in the bone marrow smear. Olaparib was not mutagenic in an Ames bacterial mutation test, but was clastogenic in a Chinese Hamster Ovary (CHO) chromosome aberration test in vitro. In rats, oral dosing of olaparib prior to mating produced no adverse effects on male fertility or conception. However, embryo fetal survival was decreased. In embryo fetal development studies in rats, administration of olaparib during organogenesis caused reductions in early embryo-fetal survival and fetal weights, as well as increased in visceral and skeletal abnormalities and major eye and vertebral/rib malformations.

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AZD6738

In preclinical models, pharmacodynamic activity of AZD6738 manifested as modulation of CHK1 phosphorylations (signaling events downstream of ATR) and increase in DNA double strand break marker γH2AX, leading to inhibition of cellular proliferation in cell line assays in vitro and growth inhibition in xenografts in vivo. Increased activity has been seen in ATM deficient compared to proficient cell lines in vitro, and this differential is translated to in vivo models in a dose dependent manner (Investigator's Brochure, current version).

AZD6738 was identified as a potent reversible ATP-competitive inhibitor of ATR kinase activity with IC50 values of 0.001 μM and 0.074. AZD6738 was screened against a 71 kinase panel including related lipid PI3K and protein PI3K-like kinases in in vitro isolated enzyme assays using 32P radioactive assays to determine potency and selectivity. A large margin of activity was observed relative to ATR enzyme isolated enzyme activity (0.001 μM) for most targets tested with the closest targets being PI3Kd at 6.8 μM (6800-fold above ATR IC50) and DYRK at 10.8 μM (10800-fold). Kinase selectivity was also determined using active- site dependent competition binding assays against 442 targets at 1 μM AZD6738 with only PI3KC2G showing any significant inhibition (20%). Broader in vitro IC50 screening against a panel of 186 additional molecular targets, AZD6738 showed significant activity on 20 targets with highest affinity at the tachykinin NK3 receptor (Ki 0.389μM). AZD6738 was screened for inhibition of closely related PI3K target pathway signaling in cell assays to determine potency and selectivity. A large margin of activity was observed for all targets tested relative to inhibition of ATR-dependent kinase signaling (0.074 μM) indicating little activity against other PI3K signaling pathways at relevant doses.

AZD6738 is a cellular inhibitor of ATR and a dose-dependent decrease in direct downstream signaling substrates such as CHK1 pSer345 are observed across cancer cell lines as measured by western blotting (Figure 5; Investigators Brochure, current version). CHK1 pSer296 (CHK1 auto-phosphorylation) is also inhibited indicating impairment of ATR-CHK1 signaling pathway. Consistent with the mechanism of action of inhibiting ATR-dependent DNA repair and increasing replication stress, AZD6738 treatment shows a corresponding increase in the DNA double strand break markers. H2AX and pSer 824 KAP1 is observed as well as damage marker CHK2 pThr68. This is only apparent at the later 24 h time point and consistent with a time delay associated with conversion of stalled replication forks into DNA double stranded breaks and accumulation of un-repaired damage.

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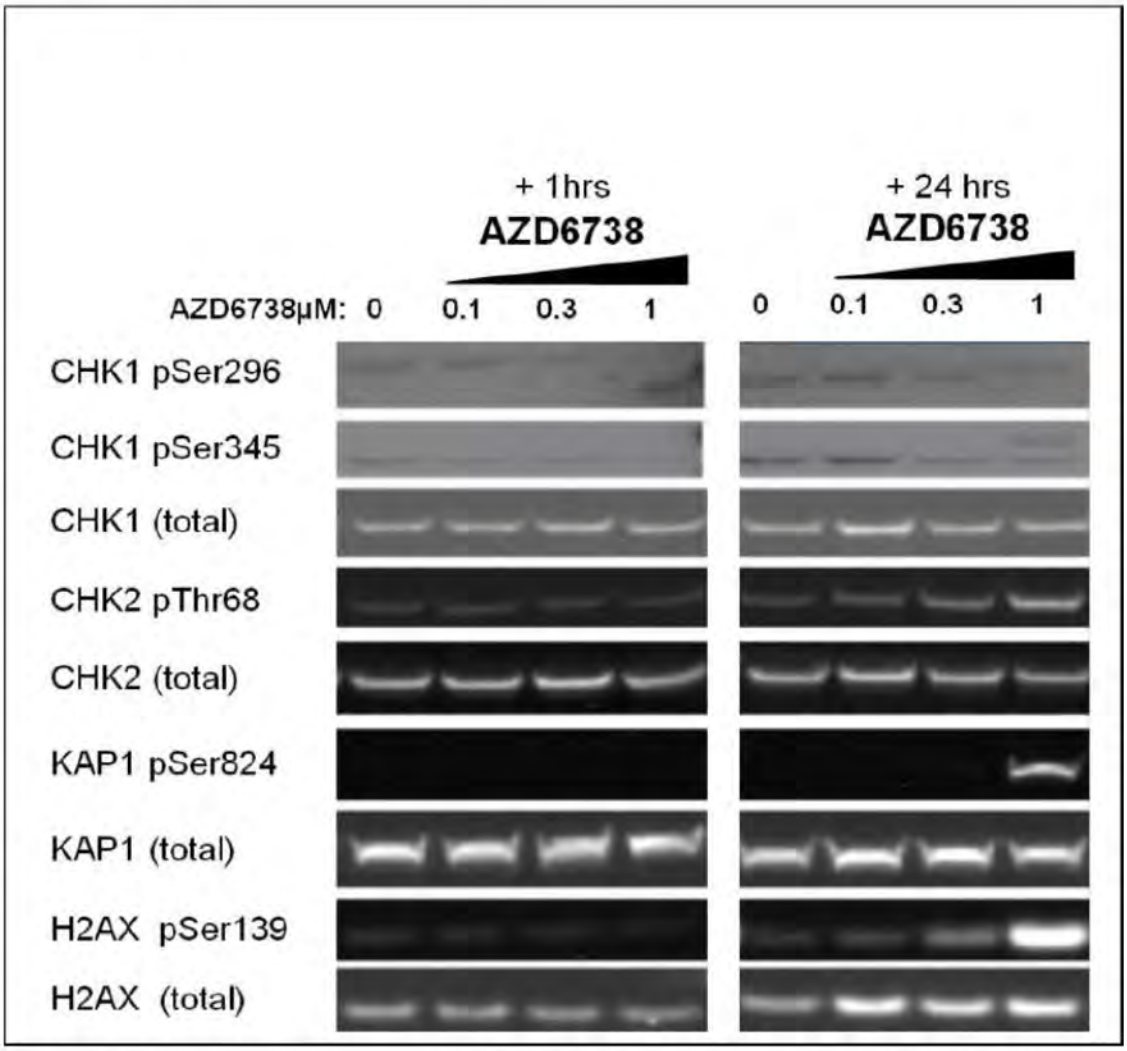


Figure 5. Protein expression of ATR/CHK1 signaling pathway with ATR inhibition in LoVo cells

AZD6738 is a potent cellular ATR inhibitor that will show activity against replicating cells. Consistent with the expected mechanism of action, flow cytometry analysis of the LoVo cancer cell line treated with AZD6738 shows a dose and time dependent increase in the accumulation of cells in S-phase of the cell cycle, indicating impaired DNA replication and cell cycle progression. An expected corresponding decrease is G1 and G2/M cell populations are observed. In addition, cell death is also suggested by the appearance of cells with low/fragmented DNA content (Sub-G1 population). Similarly, a dose-dependent rapid accumulation of γH2AX (T1/2 2.9 -8.6 h) was observed following the addition of AZD6738 as assessed by immunofluorescence staining in treated LoVo cells. An assessment of total cell number (confluency) was also conducted and AZD6738 treatment caused concentration dependent growth inhibition. In combination cell line studies with chemotherapy agents such as cisplatin, melphalan, gemcitabine, and hydroxyurea, AZD6728 shows synergistic enhancement of cell killing activity across multiple cell lines.

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In rat and dog models the rate of absorption of AZD6738 gave a C_{max} ½-4 hours post dose. In dogs, exposure was higher following repeat dosing indicating accumulation, this was not evident in rats. Metabolism occurs primarily in hepatocytes, dependent upon CYP3A4, resulting primarily in deamination of the methylsulfonimidoyl group or oxidation products. Six metabolites have been identified. Excretion has not been determined. AZD6738 inhibits P-gp, BCRP, OATP1B1, OATP1B3, MATE1, and MATE2K. No reversible or time dependent inhibition of CYP enzymes was observed. AZD6738 was predicted to achieve efficacious exposure at doses 115mg-200 mg BID in monotherapy and at 80mg BID when in combination with radiation.

A panel of safety pharmacology studies have been conducted with AZD6738. In toxicology studies, reduced food consumption and body weight loss were considered to be the dose-limiting toxicities upon repeat dosing in both rats and dogs. Emesis and loose feces were observed in the 1-month dog study at the top dose level of 10 mg/kg/day. There were small decreases in body weight gain following single doses of 30 and 100 mg/kg AZD6738 in rats. Inhibition of gastric emptying may contribute to the reductions in body weight gain. Biliary epithelial degeneration/necrosis with portal inflammatory cell infiltrates was observed in dogs at the highest dose over one month. There were no treatment related findings in the liver at the end of the recovery period. In both rat and dog models, hypocellularity was noted in lymphoid tissues. Changes in bone marrow correlated with a decrease in all cell lineages in the peripheral blood. Degenerative/atrophic changes were noted in the male reproductive tissues in rats and dogs resulting in decreased spermatozoa present within the epididymides and an increase in effete cellular debris. The lesion was still present in recovery animals one month after cessation of dosing. In female rats, reversible minimal to slight degeneration/inflammation within the corpora lutea was observed. The reproductive cycle appeared unaffected. AZD6738 caused peripheral vasodilatation, leading to decreased blood pressure and concomitant increases in heart rate and cardiac contractility. Lower blood pressure values were detected in the one-month dog study, which was reversible. The NOEL was 3mg/kg/day. AZD6738 was not mutagenic in the Ames test, but was positive in the mouse lymphoma assay in the absence of S9.

Olaparib and AZD6738

DNA damage, such as replication stress, activates ATR. ATR activation at stalled replication forks leads to suppression of replication fork origin firing promoting repair and activates S/G1/G2-cell cycle checkpoints to prevent premature mitosis and maintain genomic integrity. This allows for repair of DNA errors. Failure to resolve this damage, such as occurs with the use of ATRi, leads to genomic instability, fork collapse and with increasing degrees of DNA damage to eventual cell death. Similarly, PARPi, such as olaparib, elicit inhibition of single-strand- break repair leading to an increasing the number of single stranded DNA breaks. Additionally, "trapping" of PARP-DNA complexes creates DNA lesions. Both of these mechanisms (ssDNA breaks and "trapping" of PARP-DNA complexes) create DNA replication fork damage (replication stress) and accumulation of DNA double strand breaks. BRCA1/2 are then replied upon to repair the dsDNA breaks via homologous recombination. In BRCA1/2 deficient cells, homologous recombination is deficient (HRD) so this repair does not occur leading to cell death. Additionally, ATRi leads to loss of G2/M phase checkpoint and permits cells with high levels of dsDNA to enter mitosis prematurely. Once in mitosis the inability to appropriately partition broken chromatid fragments symmetrically due to the dsDNA breaks leads to cell death in a process known as mitotic

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catastrophe. These multiple mechanisms of increasing ssDNA and dsDNA breaks and lack of adequate repair functionality are the reason for a synergistic effect of PARPi and ATRi in the setting of HRD (Figure 6).

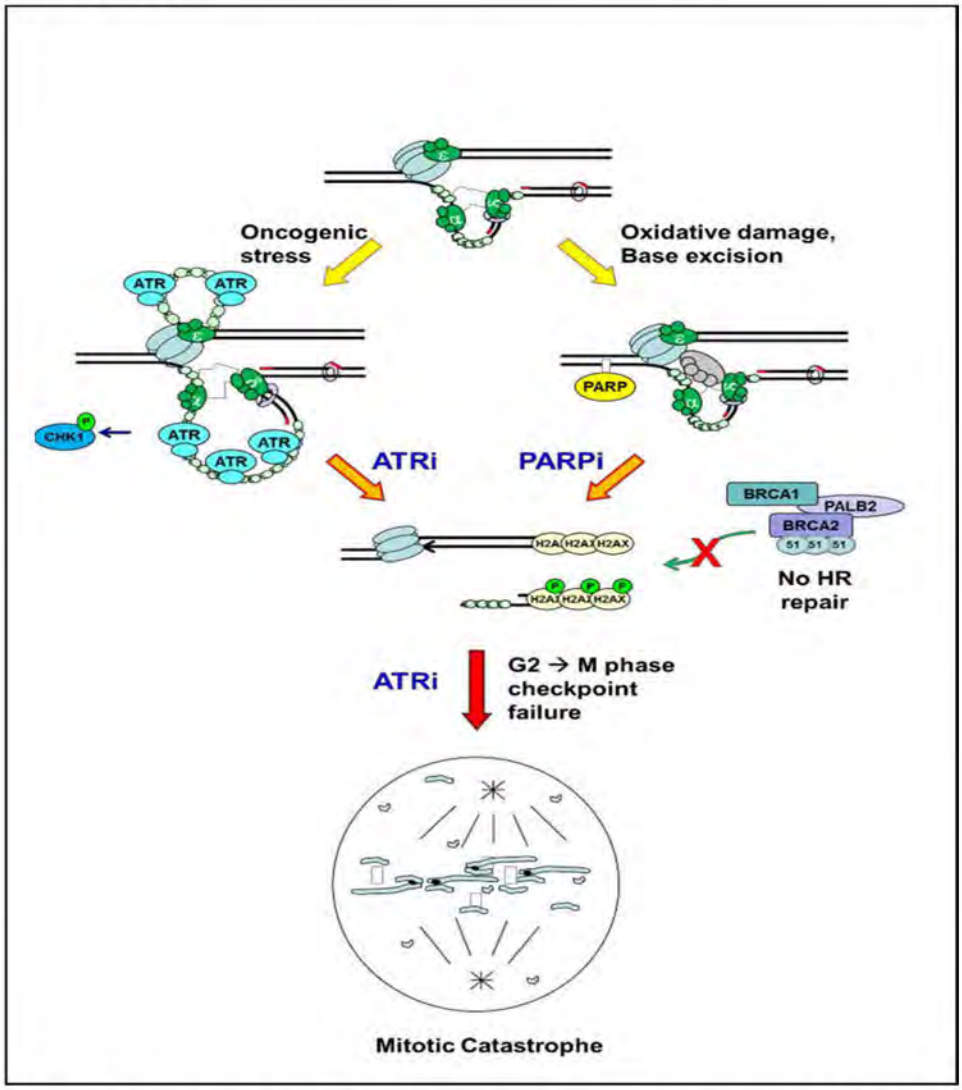


Figure 6. Diagram illustrating hypothesis for synergy with combination PARPi and ATRi

Indeed, cell lines studies in which ATM or ATR gene expression are specifically down-regulated have shown significantly increased sensitivity to PARPi (related to olaparib) when compared to their matched control cells. Consistent with these findings, cell line studies using early in vitro probe ATR inhibitor NU6027 in combination with PARP inhibitors also show significantly greater cytotoxic activity than either agent alone (Peasland et al, British Journal of Cancer, 2011). These pre-clinical findings suggest that a combination with clinically relevant ATR or PARP inhibitors such as AZD6738 and olaparib respectively could combine synergistically to achieve greater anti-tumour activity (response and/or durability) than either agent as a monotherapy.

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AZD6738 when used in a concurrent combination with olaparib across a panel of 26 unselected gastric cancer cell lines shows a significant enhancement of activity compared to single agent treatments alone using 5-day MTS end-point anti-proliferation assays (Figure 7; Investigator's Brochure, current version).

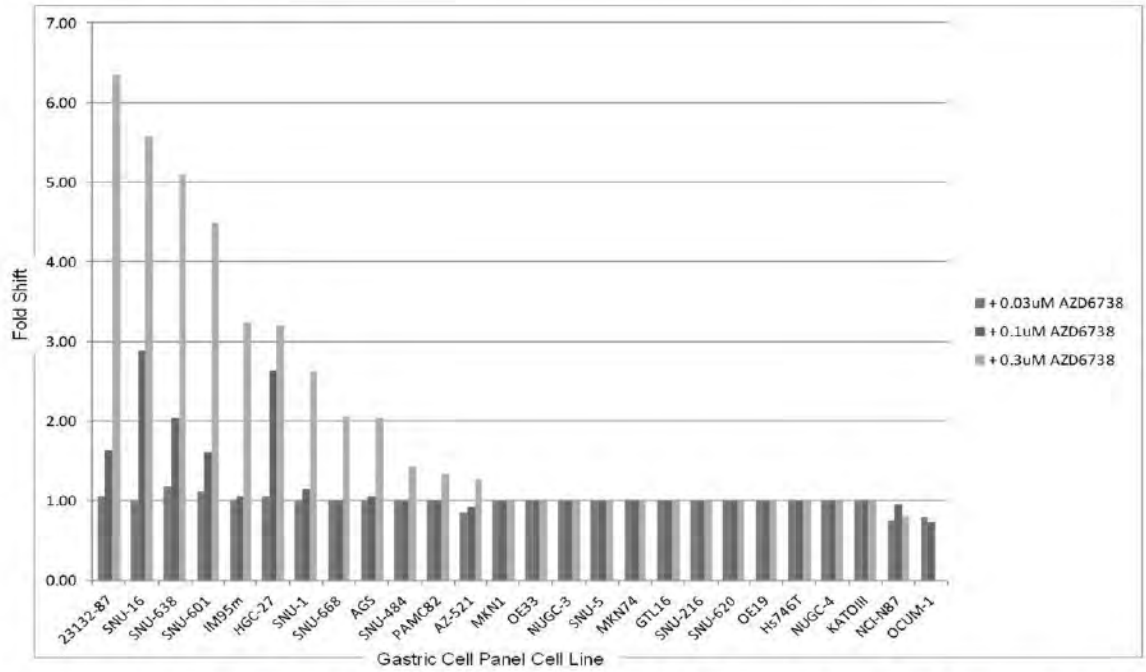


Figure 7. Fold shift in GI50 of olaparib with AZD6738 across panel of 26 gastric cell lines in vitro

Further in-depth studies of select gastric and lung cancer cell lines were performed using the Incucyte (Essen Bioscience) live cell imaging platform to monitor cell growth (and inhibition) over time. ATM-proficient gastric and lung cancer cell lines and low ATM protein expressing gastric and lung cancer cell lines were compared. Greater combination activity was observed in both low ATM expressing cell lines then the ATM proficient cell lines (Figure 8; Investigator's Brochure, current version).

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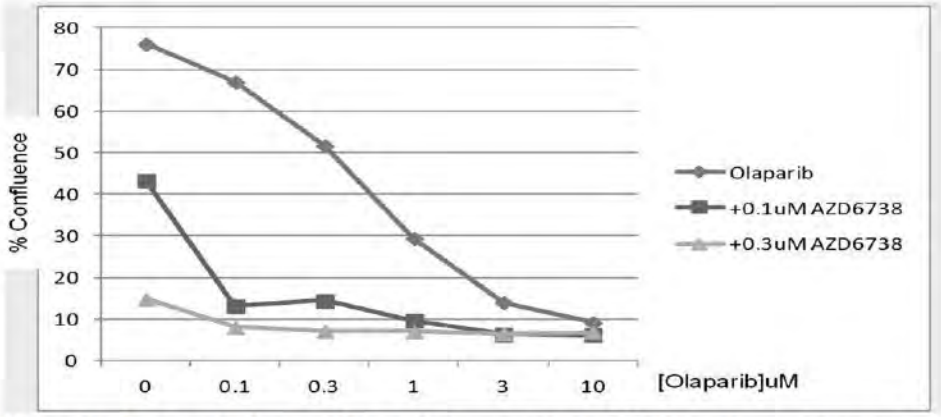


Figure 8. Incucyte live cell in vitro growth inhibition time course assays for AZD6738 and olaparib in ATM-deficient NCI-H23 lung cancer cell line in vitro

The additional data are broadly consistent with 5-day MTS assay results and further supports the hypothesis of enhanced AZD6738 and olaparib combination activity in cells with low ATM protein expression.

The combination of AZD6738 with olaparib was also examined in an HBCx-9 triple negative breast cancer primary explant model. A comparison of single agent versus combination therapy at two different dosing schedules, demonstrated a synergistic benefit to the combination, this benefit persisted even after the dosing ceased (Figure 9; Investigator's Brochure, current version).

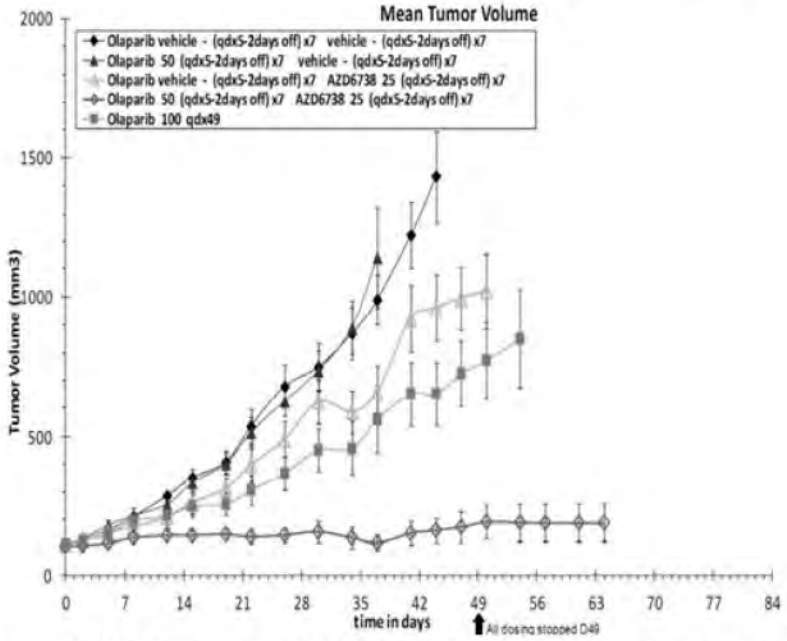


Figure 9. Anti-tumor inhibition of HBCx-9 breast cancer primary tumor xenograft model for AZD6738 used in combination with olaparib

In ovarian cancer, combination PARPi with ATRi is synergistic both *in vitro* and *in vivo*. In an ovarian cancer patient derived xenograft (PDX) model, prolonged treatment (>20 weeks) of a

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BRCA 2 mutant tumor with olaparib monotherapy results primarily in partial tumor response with no durable CR. Ovarian tumor derived from a *BRCA2* mutant carrier was transplanted to mice ovaries. When tumors reached 70mm^3, mice were treated with olaparib (MTD 100mg/kg/day) until progression (Figure 10; Kim et al, Clinical Cancer research, 2016). The majority of tumors had partial response (blue line is mean tumor growth for 5/8 mice). There were no complete responses. In addition, by 20 weeks, tumors began to increase in volume suggesting resistance (red-PDX 4, 5, and 6). Eventually, these PDX tumors become resistant to PARPi monotherapy.

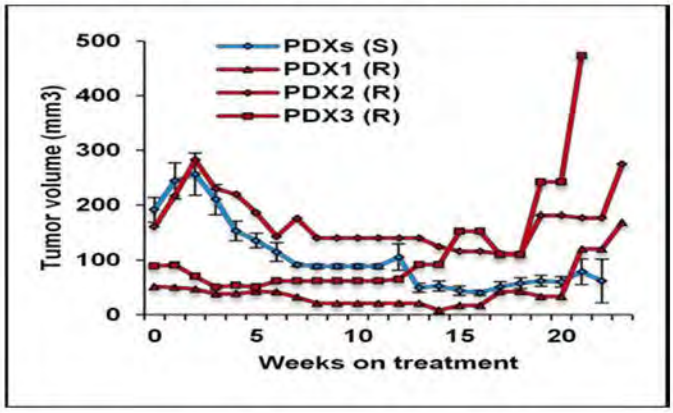


Figure 10. PARPi alone at the MTD (100mg/kg/day X 7 days) for prolonged treatment results in tumor suppression not regression in a BRCA2 mutant HGSCP PDX (WO-2)

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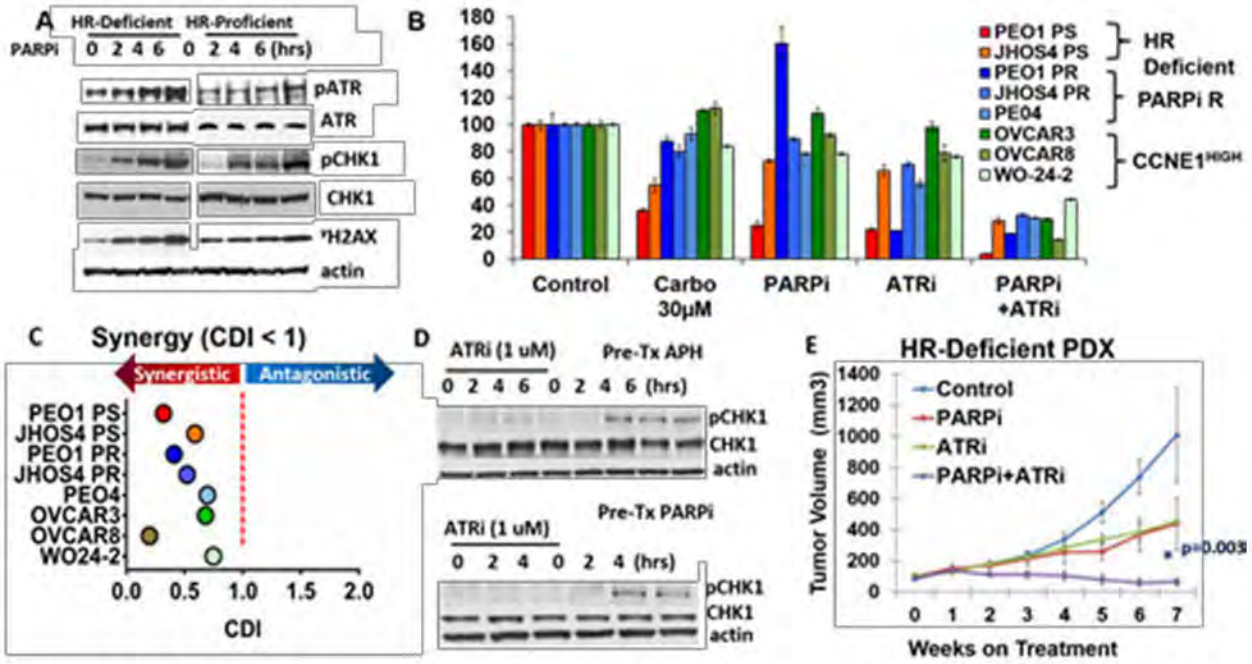


Figure 11. PARPi treatment increases ATR signaling and synergizes with ATRi in BRCAMUT, PARPi R, and CCNE1HIGH HGSOC cells and PDX tumors

A) PEO1 & PEO4 were treated with PARPi (1uM) and probed for phospho & total ATR and CHK1, γH2AX at 0, 2, 6 and 24hrs. **B**) Viability of HR-deficient (PEO1, JHOS4), PARPi R (PEO1PR), and CCNE^{HIGH} (OVCAR 3 *CCNE1* amp, OVCAR 8*CCNE1)* high-copy gain, WO-24 primary tumor culture (Cyclin E high protein) by MTT after 5 days' treatment with olaparib (1 μM), ATRi (AZD6738) (0.1-1 μM), and Both (≤ to 1 μM for each). **C**) Synergy calculations for all cell lines: CDI <1 synergy, =1 additive, >1 antagonistic. **D)** PEO1 was pre-treated with aphidocolin (APH) upper panel, and then cells were treated with ATRi or vehicle for 0, 2, 4 6 hrs and probed for phospho and total CHK1 (upper panel). PEO1 cells were then pretreated with PARPi (1 μM) for 30min and then treated with ATRi for 0, 2, 4 hrs and probed for pCHK1, CHK1. **E**) Treatment with olaparib (50mg/kg/day 1-5) and ATRi (AZD6738; 25mg/kg/ day 1-5) was initiated when tumors reached ~70mm^3. Tumor growth was assessed weekly by sonography. Mouse weights were stable for all arms, confirming tolerability. Synergy (CDI <1; p<0.003 CR).

In contrast to single agent PARPi, combination PARPi with ATRi is synergistic in both *BRCA* mutant and *BRCA* wild type *in vitro and in vivo* models. We have reported that PARPi treatment increases reliance on ATR for genome stability (Figure 11A; Kim et al, CCR, 2017), and synergizes with ATRi in killing HR-deficient (PEO1, JHSO4) and PARPi-resistant (PEO1-PR, JHOS4-PR) compared to PARPi or ATRi alone (Figure 11B, C; Kim et al. Clinical Cancer Research, 2016). Notably, PARPi-ATRi is even effective in killing platinum-resistant *CCNE1*^{HIGH} cells (OVCAR3, OVCAR8, WO-24), the most chemotherapy-resistant subset of HGSOC. AZD6738 (1 μM) blocks the phosphorylation of CHK1 (Figure 11D; Kim et al, Clinical Cancer Research, 2016) triggered by either DNA polymerase inhibition (upper panel) or PARPi treatment (lower panel). *Importantly, combination of PARPi with ATRi leads to complete ovarian tumor regression in an HR-deficient PDX model (*Figure 11*E). Such responsiveness is not achievable*

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with the maximum dose of PARPi alone, which correlates with response rates to PARPi single-agent therapy seen in the clinic (Figure 11E; Kim et al, Clinical Cancer Research, 2016). Thus, PARPi-ATRi may similarly increase complete and durable responses in the clinic.

Although ATRi or PARPi treatment each cause replication fork collapse into DSBs, the mechanisms by which they cause these breaks are different. PARP helps ligate single-stranded breaks (SSBs), which occur spontaneously at 20,000-50,000 sites per genome per day. When left unrepaired because of PARPi treatment, these SSBs are converted into DSBs during DNA replication. In contrast, ATR prevents DSB formation by making the replication fork less vulnerable to endonuclease attack. Therefore, inhibition of these distinct genome stabilizing mechanisms *together* increases DSB generation (Figure 12; Kim et al, Clinical Cancer Research, 2016), apoptosis (Figure 12) and cancer regression (Figure 11E).

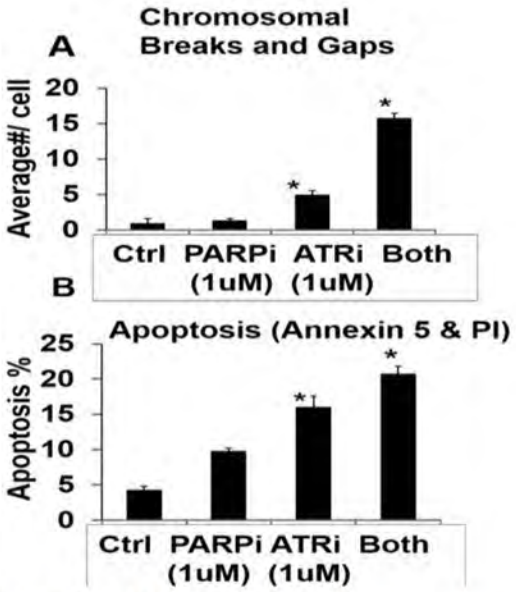


Figure 12. PARPi-ATRi combination increases chromosomal DSBs leading to apoptosis

A) PEO1 cells were treated with indicated drug for 14 hrs. Nocodazole (0.5 μM) was added for 3 hrs prior to harvest to arrest cells in mitosis. Cells were fixed, and chromosomes were stained with Giemsa. Gaps and breaks of chromosomes were counted (50 spreads in each group were counted and average number of gaps and breaks per cell was calculated. **B**) PEO1 cells were treated for 48 hrs and apoptosis evaluated by Annexin 5 and PI by FACS. (*ATRi alone vs Both, p=0.0005 for gaps/breaks; p=0.009 for apoptosis).

CCNE1^{HIGH} HGSOCs have the worse overall survival and often exhibit *de novo* relative platinum-resistance[11,46], thus, treatment options are limited. We show that PARPi-ATRi results in tumor regression compared to monotherapies in a *CCNE1*-amplified PDX model developed from a patient with platinum-resistant disease (Figure 13A; Kim et al, Clinical Cancer Research, manuscript in preparation). Notably, PARPi-ATRi treatment increased survival by 2-fold from 4

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to 8-9 weeks (Figure 13A). While this response offers some promise to affected patients, resistance to PARPi-ATRi was ultimately acquired in these tumors, as well as in two cells lines after 2 years of continuous selection in culture. *These novel models will allow us to characterize the impact of these resistance mechanisms on durable response to a cutting-edge genotoxic therapy, PARPi-ATRi.*

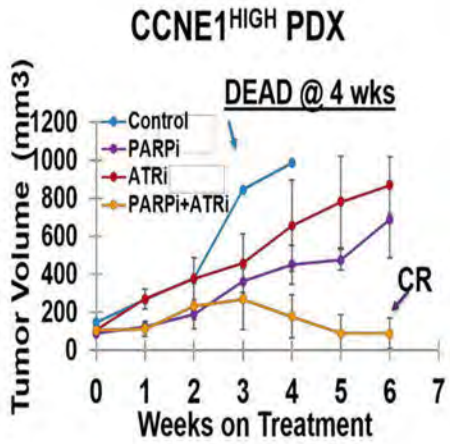


Figure 13. PARPi-ATRi causes tumor regression and extends disease-free interval in platinum - resistant CCNEHIGH PDX, but resistance ultimately results Tumor from patient with recurrent, platinum- resistant HGSOC with *CCNE1* amplification used to develop PDX. Once PDX tumors reached 70-100 mm^3, mice randomized to vehicle, PARPi (50 mg/kg/day, ATRi (AZD6738 50 mg/kg/day) each Day1-5 and PAPRi-ATRi (same doses). Three mice/grp. PDX tumors were measured by sonogram.

These data support combined DNA repair and cell cycle checkpoint inhibition as a promising direction for recurrent ovarian cancer. Studies in NSG mice show that dosing of 50mg/kg olaparib 1 hour before 25 mg/kg AZD6738 once daily on an intermittent 3 day on/4day off or 5 day on/2 day off weekly cycle was well tolerated with no adverse effects on body weights or other clinical signs.

2.3 Toxicology and safety pharmacology summary

Olaparib

As of Q3 2016, approximately 5670 patients with ovarian, breast, pancreatic, gastric, and other solid tumors are estimated to have received treatment with olaparib either as a monotherapy or in combination with chemotherapy or other anti-cancer agents (Investigator Brochure, current version). The recommended monotherapy tablet dose is 300mg twice daily. Monotherapy remains generally well tolerated at this dose.

The olaparib tablet is rapidly absorbed with peak plasma concentrations of approximately 1.5 hours (Investigator's Brochure, current version). Following time to maximum plasma concentration, plasma concentrations of olaparib declined in a biphasic manner with an average terminal elimination $t_{1/2}$ of 14.9 hours (Sd 8.2 hours). The mean apparent oral plasma clearance was approximately 7.4 L/h (Sd 3.9 L/h). The mean volume of distribution was greater than total body

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water indicating that olaparib was distributed into the tissues. Multidose data indicates that the PK of olaparib is time-dependent. The AUC for olaparib increases approximately proportionally with dose and for C_{max} for slightly less than proportionally with dose. Studies of the relative single-dose bioavailability of the capsule versus tablet formulations showed that at the two lower tablet doses the C_{max} with the tablet formulation tended to be slightly higher and the AUC was similar. However, at the highest tablet dose (250mg), the exposure delivered by the tablet formulation was higher than that delivered by the 400mg capsule. The tablet and capsule formulations cannot therefore be considered bioequivalent. Olaparib is metabolized via hydroxylation and opening of the cyclopropyl ring (M12), mono-oxygenation of the flurophenyl ring (M15) and dehydrogenation of the piperazine ring (M18) and excreted as up to 37 drug related component in the urine (35-50%) and up to 20 in the feces (12-60%). The largest percentage of excreted product in the urine and feces was unchanged olaparib.

Toxicities considered associated with administration of olaparib include hematological effects, decreased appetite, nausea, vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, and dizziness. In a pooled analysis of 766 patients with advanced solid tumors on 400mg capsule olaparib, 45.3% experience a Grade 3 or higher serious adverse event with 1.8% experiencing an adverse event with the outcome of death. Grade 3/4 anemia occurred in 11.5%, fatigue in 6.9%, nausea in 2.7% and vomiting in 3.3%. The fatal AEs were due to acute leukemia, bone marrow toxicity, myelodysplastic syndrome, cerebrovascular accident, chronic obstructive pulmonary disease, sepsis, hydronephrosis and pleural effusion, intestinal perforation, and pulmonary embolism. Only 5.9% of patients discontinued treatment due to adverse events. Combination studies resulted in lower maximum tolerated dose compared with monotherapy, particularly due to increases in myelotoxicity. In patients with creatinine clearance 31 to 50 mL/min, AUC increased 44% and C_{max} by 26% compared with patients with normal renal function. Therefore, dose adjustment for renal function abnormality is recommended. Olaparib is not recommended for use in patients with moderate or severe renal failure. For patients with moderate or severe hepatic impairment based on Child-Pugh score, olaparib is not recommended. No data are available for patients over 75 or in pediatric patients. There is no data in obese or underweight patients. 94% of patients who have enrolled on olaparib trials have been Caucasian and thus there is insufficient data to evaluate potential effect of race on olaparib PK. There is no major effect of food on C_{max} or AUC_{0-24} unless it was a high fat meal and then there was a 21% decrease in C_{max}.

AZD6738

AZD6738 is rapidly absorbed following oral dosing in fasting conditions, with a peak plasma concentration observed typically after 1.5 hours post dose and declining in a biphasic manner with a typical elimination half-life of ~11 hours (Investigator's Brochure, current version). Despite a high inter-individual variability (60%-70%), there was an apparent dose proportional increase in AZD6738 plasma concentrations across the tested doses. The limited data did not show a significant difference in PK when AZD6738 was administered as monotherapy or in combination with olaparib and carboplatin.

In the patients treated with AZD6738 monotherapy, thrombocytopenia and anemia were the common adverse events. The timing of nadirs is a matter of ongoing investigation.

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2.4 Clinical experience

Olaparib

Olaparib was approved by the US FDA in December 2014 for use in patients with recurrent ovarian cancer who have failed three prior lines of chemotherapy and who harbor one or more deleterious or suspected deleterious germline mutations in *BRCA*. To date olaparib has been studied as a monotherapy and in combination with chemotherapy and other anti-cancer agents, particularly in patients with tumor enriched for HRD (Investigator's Brochure, current version). In August 2017, the FDA approved olaparib tablets for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum- based chemotherapy.

Multiple phase II monotherapy studies have been completed demonstrating the safety of olaparib in a growing cohort of patients and also establishing monotherapy response rates (Investigator's Brochure, current version). These rates differ for patients with ovarian carcinoma by platinum sensitivity, number of prior regimens, and germline *BRCA* status. For instance, in a cohort which included patients who experienced recurrence within 1 year of prior platinum, had a median number of prior chemotherapy regimens of 3, and who received a capsule dose of 400mg twice daily, overall response rate was 31% with a median duration of 6.8 months. A summary table of five additional monotherapy trials in patients with g*BRCA* mutations summarizes overall response rates and duration of response (Table 1; Investigator's Brochure, current version)

Table 1. Summary of key efficacy variable in studies D0810C00002, D0810C00009, D0810C00020, D0810C00024 (ovarian cancer)

	Study D0801C00042 Ovarian cohort	Study D0810C00020 Phase II relapsed ovarian and breast cancer study Ovarian Cohort	Study D0810C00009 Phase II *gBRCA* ovarian proof-of-concept study		Study D0810C00024 Phase I formulation comparison study		Study D0810C00002 Phase I FTIM study
	Olaparib 400 mg bd (n=193)[a]	Olaparib 400 mg bd (n=64)[b]	Olaparib 100 mg bd (n=24)[c]	Olaparib 400 mg bd (n=33)[c]	Group 1 – olaparib 400 mg bd capsule (n=7)[d]	Group 6 – olaparib 400 mg bd capsule (n=13)[d]	All olaparib doses combined (n=49)[e]
Median PFS (months)	7.0	7.2	1.9	5.8	6.6	NR	3.8 (TTP)[e]
ORR (%)	35.9[f]	28.1[g]	12.5	33.3	14.3	38.5	24.5[e]
Median DoR (months)	7.4	9.1	8.8	9.5	NR	NR	NR

a Pre-specified subset of overall study population (patients with *gBRCA* mutated ovarian cancer).
b Pre-specified subset of overall study population (patients with *gBRCA* mutated or high-grade serous/undifferentiated ovarian cancer).
c Overall study population (patients with *gBRCA* mutated ovarian cancer).
d Subgroup of patients with *gBRCA* mutated ovarian cancer in Groups 1 and 6 of Study D0810C00024 who received olaparib 400 mg bd capsules.
e These are results for the pre-specified subgroup of patients with *gBRCA* mutated ovarian cancer.
f This is the ORR in the Measurable Disease Analysis Set (n=167).
g This is the ORR in the overall ovarian cancer patient population; ORR in *gBRCA* mutated ovarian cancer patients was 41%.
bd Twice daily; *BRCA* Breast cancer susceptibility gene; CA-125 Cancer Antigen-125; DoR Duration of response; FTIM First time in man; *gBRCA* Germline *BRCA*; NR Not reported; ORR Objective response rate; PFS Progression-free survival; RECIST Response Evaluation Criteria in Solid Tumours; TTP Time to progression.

Eleven combination studies, particularly with platinum agents, have been completed at the phase I and II level, including with topotecan, cisplatin, gemcitabine, liposomal doxorubicin, paclitaxel, carboplatin and most recently cediranib. Maintenance therapy has also been investigated in a

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randomized phased 2 trial, to be used following platinum based chemotherapy for platinum sensitive ovarian cancer. A PFS benefit (8.4 vs 4.8 months, $p<0.001$) was seen. Most notably, a benefit was seen even in those patients without a germline BRCA mutation.

AZD6738

AZD6738 has been used in four clinical protocols (Investigator's Brochure, current version):

- A Phase I study in patients with chronic lymphoid leukemia, closed due to failure of recruitment;
- A Modular, Phase I, two part open-label study of combination ADZ6738 with carboplatin, olaparib, or Durvalumab (MEDI4736), ongoing (D5330C00004);
- A Phase I monotherapy dose escalation in advanced solid tumors (Part A), followed by a monotherapy expansion ATM-deficient advanced solid tumors (Part B) and a radiotherapy combination expansion arm (Part C), ongoing (PATRIOT / D5330C00002);
- Dose escalation study of AZD6738 in combination with paclitaxel in advanced solid tumour patients, ongoing (Pre-VIKTORY).

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 carboplatin and olaparib. Events of thrombocytopenia (sometimes accompanied by neutropenia which can arise late, even after day 30, have resulted in dosing delays in patients who were receiving AZD6738 plus carboplatin. These were deemed schedule limiting toxicities, rather than dose limiting toxicities as the main issue appeared to be delay in the recovery of the platelets. In addition, the toxicities associated with the combination of carboplatin and AZD6738 appear to be cumulative as the bone marrow effects become more severe as more cycles of therapy are given. Seven dose cohorts were explored in the carboplatin combination and 32 evaluable patients were recruited. The maximum tolerated dose and schedule of AZD6738 in combination with carboplatin AUC 5 was found to be 40mg orally once per day for two consecutive days starting on the day of the carboplatin dosing.

Eleven dose cohorts evaluated the combination of AZD6738 plus olaparib and 52 evaluable patients were recruited. The dose limiting toxicities were anaemia, neutropenia and thrombocytopenia. Given that olaparib is an approved drug in ovarian cancer and response rates to monotherapy olaparib are known to be lower at sub-optimal doses, a key objective was to identify a combination dose and schedule at the approved monotherapy tablet dose of olaparib, which is 300 mg BID. The recommended Phase 2 dose of this combination is 300 mg BID olaparib and 160 mg QD AZD6738 days 1-7 on a 28-day cycle.

The dosing schedule of 7 days on, 21 days off AZD6738 within each treatment cycle was supported by the PK-pharmacodynamics (PDx) model of thrombocytopenia, predicting a period of 21 days free of drug to achieve a full platelet recovery. The recommended dose 160 mg QD was predicted to maintain AZD6738 mean steady state concentrations above the estimated IC90 threshold (based on ATR enzyme inhibition assay in LoVo cells) and the GI90 threshold (based on the cellular growth inhibition activity in LoVo cells) across the full dosing interval i.e. 24h. Please refer to AZD6738 IB for further information around the *in vitro* threshold values. In addition, this daily

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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, 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 160 mg QD D1-7 was driven by maintaining maximally active exposure consistent with manageable safety.

Details on the latest non-clinical and clinical safety and efficacy data for AZD6738 are presented in the latest version of the AZD6738 Investigator's Brochure. The dose-finding study of AZD6738 and Durvalumab is ongoing, and at the time of this writing a recommended Phase 2 dose has not been identified. The Phase I monotherapy study has completed 5 cohorts and recruited 24 evaluable patients. A recommended Phase 2 dose of 160 mg PO BID AZD6738 has been identified and expansion cohorts are ongoing that are examining different intermittent dose schedules. The clinical experience has found that successive dose cycles have resulted in toxicities beyond cycle 1, requiring drug holidays to allow the bone marrow to recover. Presently, the study is examining a 14 days on, 14 days off schedule (at 160 mg BID AZD6738).

The Phase I paclitaxel combination is currently on cohort 4, with paclitaxel dosed at 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. AZD6738 has been dosed on days 1-21 at 40, 60, and 80 mg QD, with the latter cohort having 1x DLT of Gr 3 febrile neutropenia. This prompted a change to the AZD6738 schedule to "front-load" the AZD6738 exposure to days 1-7, at 160 mg QD, as per the olaparib combination. At the time of this writing, a recommended Phase 2 dose has not been identified.

Olaparib and AZD6738

The combination of Olaparib and AZD6738 has been administered to 52 patients with advanced malignancy with the goal of establishing the dosing schedule (Investigator's Brochure, current version). The patients on study included 4 with ovarian carcinoma. **The recommended Phase 2 dose was established as 160 mg QD AZD6738 days 1-7 in combination with 300 mg BID olaparib on a 28-day cycle.** At 160 mg QD, >90% of patients achieve a target exposure greater or equal to that required to inhibit 90% of ATR kinase (based on in vitro data from the LoVo cell line model) for 12 hours in a 24-hour period at steady state. To date, three confirmed partial responses have been reported, 2 patients with triple negative breast cancer with germline *BRCA1* mutations and 1 patient with ER positive breast cancer and a germline *BRCA2* mutation. In all, 7 patients with triple negative breast cancer and 4 further cases of breast cancer have been included on study. Twenty cases of stable disease as best response have also been reported.

FTT PARPi tracer (University of Pennsylvania ONLY)

In a companion protocol (#823234), we are investigating a method for predicting HRD in ovarian cancer using a PET–labeled PARPi probe, 18F-fluorthanatrace (FTT). We will correlate FTT uptake and response to PARPi +/- ATRi. (University of Pennsylvania only). This study will use a separate companion protocol and informed consent form. This study is in collaboration with David

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Mankoff and Robert Mach at the University of Pennsylvania. See IRB approved protocol #823234. Patients from this study will be offered to participate in the FTT study at the University of Pennsylvania.

2.5 Research hypothesis

The therapeutic inhibition of ATR and PARP will clinically benefit subsets of patients with recurrent ovarian cancer. We hypothesize that combination PARP inhibition with ATR inhibition will be more effective in recurrent platinum sensitive and resistant ovarian cancer than traditional responses to olaparib monotherapy.

2.6 Rationale for conducting this study

For the majority of women with high-grade serous ovarian cancer (HGSOC), their disease presents at an advanced stage and is sensitive to adjuvant chemotherapy. However, for the majority of women, their disease recurs. Ovarian cancers become resistant to chemotherapy and patients ultimately die from disease. In the last decade, there has been considerable progress in understanding the genetics of ovarian cancer, but to date this knowledge has not translated into comparable survival benefit for patients. Thus, there is an urgent need for more active and less toxic interventions for recurrent HGSOC. The introduction of poly (ADP-ribose) polymerase inhibitors (PARPi) has led to new therapeutic opportunities which have yielded non-curative treatments, leaving room for novel therapeutic strategies. One such approach to improve the therapeutic index of PARPi and modulate DNA repair activity in HGSOCs is to interfere with cell cycle checkpoint signaling at targets such as ATR. ATR-CHK1 pathway blockade inhibits cell cycle arrest, resulting in progressive DNA damage, replication catastrophe, and cell death. Preclinical data in ovarian cancer demonstrates a synergistic interaction between PARPi and ATRi, which leads to tumor regression (Kim et al, CCR, 2017). Mechanistic plausibility and this preclinical data form the conceptual backbone of this Phase II pilot study. The exploratory objectives are designed to maximize understanding of the interplay between PARPi and ATRi. This will be done by examining biochemical and genomic changes in the DNA damage repair and cell cycle check point pathways and investigating new methods for predicting HR- deficiency.

2.7 Benefit/risk and ethical assessment

Epithelial ovarian carcinomas recur for the vast majority of patients and are then incurable. Thus, the goal of treatment is to prolong overall survival while maintaining a good quality of life for patients. Cytotoxic chemotherapy has a limited role in prolonging overall survival and comes with significant impacts on quality of life. Thus, new innovative strategies are needed. PARPi is one such approach. Studies demonstrate that use of PARPi can increase the time to recurrence in the maintenance setting as well as increase progression free survival in the recurrent disease setting in both HR deficient and proficient HGSOCs (rucaparib package insert, Dec, 2016; nirapaib package insert, March, 2017; and Investigator's Brochure, current version). Despite this, they do not lead to cure and therefore there is room for improvement. Combination with ATRi offers one possible mechanism to build on the success of PARPi. This study is designed to test the efficacy of the combination using a Simon two- stage design. The risk of the study derives from the fact that the safety profile of the combination has not been fully determined and the benefit of the combination treatment is untested in this patient population. As a result, prior to expanding the platinum-

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sensitive (Cohort A) and platinum resistant (Cohort B) cohorts to the maximum of 37 patients each, the safety data will be reviewed alongside the efficacy response data in the interim analysis to ensure the risk benefit ratio supports expansion. Additionally, side effect profile will be followed closely with each cycle of chemotherapy. Management of toxicities will be based on the management strategies employed with olaparib. In order to mitigate risk, women of childbearing age will be excluded from the study.

3 STUDY OBJECTIVES

3.1 Primary objectives

1. To determine the safety and tolerability of combination AZD6738 and olaparib in recurrent ovarian cancer patients using Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) for all Cohorts (e.g. Cohorts A, B, C, and D).
2. To determine the objective response rate (CR+PR) of the combination of AZD6738 and olaparib in women with recurrent ovarian cancer in platinum-sensitive and resistant, and PARP inhibitor resistant cohorts (e.g. Cohorts A, B, C, and D).
3. To determine the maximum tolerated dose (MTD) and response rate of an alternative dose and schedule of this combination using a higher dose of AZD6738 and a lower dose of olaparib (in Cohort D) than that tested in Cohorts A to C.

3.2 Secondary objectives

To determine the progression-free survival (PFS) of combination AZD6738 and olaparib for all Cohorts.

3.3 Exploratory objectives

1. Determine the response rate of AZD6738 and olaparib in a small subset of PARPi resistant (platinum-sensitive) patients with recurrent ovarian cancer (Cohorts C and D).
2. Determine the response rate of the alternative "AZD6738 high/olaparib low" schedule in a small subset of PARPi resistant (platinum-sensitive) patients with recurrent ovarian cancer (e.g. Cohort D).
3. To determine genetic and protein changes in the DNA damage repair and cell cycle check point pathways in tumor and PBMCs in response to treatment (WES, RNA seq, Q-MS).
4. To explore changes in peripheral immune characteristics before and after therapy.
5. To study cell-free DNA changes in response to treatment.
6. To investigate a method for predicting HRD in ovarian cancer using a PET–labeled PARPi probe, 18F-fluorthanatrace (FTT) and correlate with response to PARPi +/- ATRi. (University of Pennsylvania only; using a separate companion protocol and informed consent form; in collaboration with David Mankoff and Robert Mach at the University of Pennsylvania).

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4 STUDY PLAN AND PROCEDURES

4.1 Overall study design and flow chart

This is an open label, non-randomized two-stage Phase II study to examine activity of the combination of AZD6738 and olaparib in 4 cohorts of approximately 86 subjects:

Cohort A: Recurrent platinum-sensitive ovarian cancer (progression greater than 6 months from last receipt of platinum-based chemotherapy), n=37 with interim analysis after 17 subjects.

Cohort B: Recurrent platinum-resistant ovarian cancer (progression ≤6 months of the last receipt), n=37 with an interim analysis after 12 subjects.

Cohort C: PARP inhibitor (PARPi) resistant (subjects who have progressed on a PARPi), patients must be platinum-sensitive, and have a germline or somatic BRCA mutation or an HRD mutation. n=12.

The cohorts will be open concurrently and treatment assignment will be based on platinum and PARP sensitivity.

Cohorts A to C ONLY

All subjects will receive the combination of AZD6738 and olaparib. Subjects will receive olaparib 300 mg BID continuously in combination with AZD6738 at 160 mg QD Days 1-7 in a 28-day cycle. Each cycle begins upon administration of study drug on Day 1 of each cycle. Prior to the initiation of this study, it is expected that there will be less than 100 subjects treated with the combination in a Phase I trial and most of these will be subjects with gastric cancer. Thus, there will not be extensive prior experience with the combination in ovarian cancer and the safety profile of the combination has not been fully determined. As a result, prior to expanding the platinum-sensitive (Cohort A) and platinum-resistant (Cohort B) cohorts to the maximum of 37 subjects each, the safety data will be reviewed alongside the efficacy response data in the interim analysis to ensure the risk-benefit ratio supports expansion.

Cohort D: Development of an alternative dose and schedule of the AZD6738 and olaparib combination.

Part I will investigate an alternative dose and schedule of AZD6738 and olaparib using a higher dose of AZD6738 and a lower dose of olaparib, in patients with advanced recurrent ovarian cancer suitable for treatment with this combination. Patients will be platinum sensitive/platinum resistant ovarian cancer. Patient may or may not have received prior PARPi and will be enrolled irrespective of their *BRCA* status. The number of subjects treated will depend on the number of dose levels explored with a minimum of 12 subjects up to 30 subjects. **Part II** will recruit patients with ovarian cancer who are PARP inhibitor (PARPi) resistant (patients who have progressed on a PARPi. Patients must be platinum-sensitive and have a germline or somatic *BRCA* mutation or an HRD mutation n=12. This cohort will use the alternate dose and schedule, as determined in Part I. In Cohort D Part I, the alternative dose and schedule will be derived by exploring the safety and tolerability of 3 different regimens of the combination (see below), using a dose of olaparib (< 300 mg BID), while sequentially increasing the number of days and dosing of AZD6738 (from 7 to 14 days, Level 1) and increasing the daily dose (from 160 mg QD to 160 mg BID. We anticipate that

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Part I will examine all 3 dose levels before determining MTD, but other doses and schedules may also be explored if all 3 dose levels are not tolerable (e.g., level 4 or level 5, Table 3) or if the MTD is lower the highest dose of three dose levels explored.

Rationale for Cohort D:

The rationale for exploring an alternative dose and schedule of AZD6738, is that a higher dose of AZD6738 may be needed to drive reversal of resistance to PARP inhibitors than that established in AstraZeneca Study 4 (D5330C00004). The Study 4 dose and schedule of AZD6738 and olaparib is expected to drive responses in patients with platinum-sensitive and platinum-resistant disease who are PARPi naïve or did not receive PARPi as part of their last line of therapy. However, this schedule may not be as effective in patients who are PARPi-resistant, having progressed on PARPi as part of their last line of treatment. This is supported by recent pre-clinical experiments, which show that higher doses of AZD6738 drive better responses in PARPi-resistant models in vivo (Simpkins et al, Nature Communications, July, 2020.

PARPi resistant OVCA tumor bearing PDX models derived from patients with germline BRCA mutations show increased response rates to dosing schedules using concomitant dosing of PARPi (olaparib) with ATRi (AZD7838). Dosing of olaparib (when in combination with AZD6738) can be decreased to 75 mg/kg D1-6 (100mg/kg MTD in mice) which is equivalent to approximately 100-150mg BID dosing in humans. In addition, ATRi dosing when in combination with olaparib required in mice for tumor regression is 40-50mg/kg D1-6 which is equivalent to approximately 160 mg QD in humans (Simpkins et al, Nature Communications, July, 2020). ATRi, AZD6738 is well tolerated as monotherapy 160 BID D1-14 of a 28-day cycle. Also, AZD6738 is tolerable at 240 mg BID on D1-14 with durvalumab continuous (PD-1 inhibitor; no overlapping toxicities) (From communications with AZ Sept, 2019). We will investigate an alternative dose and schedule of AZD6738 and olaparib using a higher dose of AZD6738 and a lower dose of olaparib, in patients with advanced recurrent ovarian cancer suitable for treatment with this combination.

We believe that these data support: 1) determination of an alternative dose and schedule of the AZD6738 and olaparib combination, using a higher dose of AZD6738 and a lower dose of olaparib (Cohort D Part I) and testing the derived schedule in a small expansion cohort of N= 12 PARPi-resistant patients (Cohort D Part II).

Prior clinical experience of different regimens of olaparib and AZD6738

The combination of AZD6738 and olaparib has been explored in ten cohorts of up to N= 6 patients each (Table 2) in AstraZeneca Study 4 (D5330C00004). The dose of olaparib explored is 100-300 mg BID continuous and AZD6738 is 60 to 240 mg QD, with various numbers of dosing days in a 28-day cycle. Our proposition is to reduce the olaparib backbone to 100 mg BID continuous (which is still expected to be clinically active and demonstrated to trap PARP on DNA thereby causing replication stress) and increase exposure to AZD6738, in the first instance by extending the number of days dosing (from 7 to 14) and thereafter increasing the daily dose (from 160- 240 mg).

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Previous clinical experience found that 160 mg QD AZD6738 days 1-7 and 100 mg BID olaparib continuous was tolerated on a 28-day cycle (Cohort 2 in Table 2) and based on treatment of 19 patients in ARMS A-C of the CAPRI. The "target dose" of 14 days AZD6738 at 160 mg BID was tolerated chronically in a monotherapy clinical study and there is further evidence that 240 mg BID for 14 days may be tolerated (in combination with durvalumab, an anti-PD-L1 antibody that has non-overlapping toxicity with AZD6738). In addition, 160 mg BID achieves near maximal PD effect in clinical studies, indicative of optimal ATR inhibition, as assessed by reductions in platelets and monocytes, which is believed to represent on-target toxicity. The planned cohorts are shown in Table 3.

Table 2. Dose Cohorts explored in AstraZeneca Study 4 (D5330C00004)

Cohort number	Dose of AZD6738	Dose of olaparib	Tolerability
1	60 mg QD Days 1-5 + Days 15-19	100 mg BID continuous	Tolerated (no DLTs in N= 6)
2	160 mg QD Days 1-7	100 mg BID continuous	Tolerated (no DLTs in N= 6)
3	80 mg QD Days 1-7	200 mg BID continuous	Tolerated (no DLTs in N= 6)
4	160 mg QD Days 1-7	200 mg BID continuous	Tolerated (no DLTs in N= 6)
5	160 mg QD Days 1-14	200 mg BID continuous	Not tolerated
6	160 mg QD Days 1-7	300 mg BID continuous	Tolerated & declared Ph2 dose & schedule
7	240 mg QD Days 1-7	300 mg BID continuous	Not tolerated
8	80 mg QD Days 1-14	300 mg BID continuous	Tolerated (no DLTs in N= 6)
9	160 mg QD Days 1-10	300 mg BID continuous	Not tolerated
10	120 mg QD Days 1-10	300 mg BID continuous	Tolerated (no DLTs in N= 6)

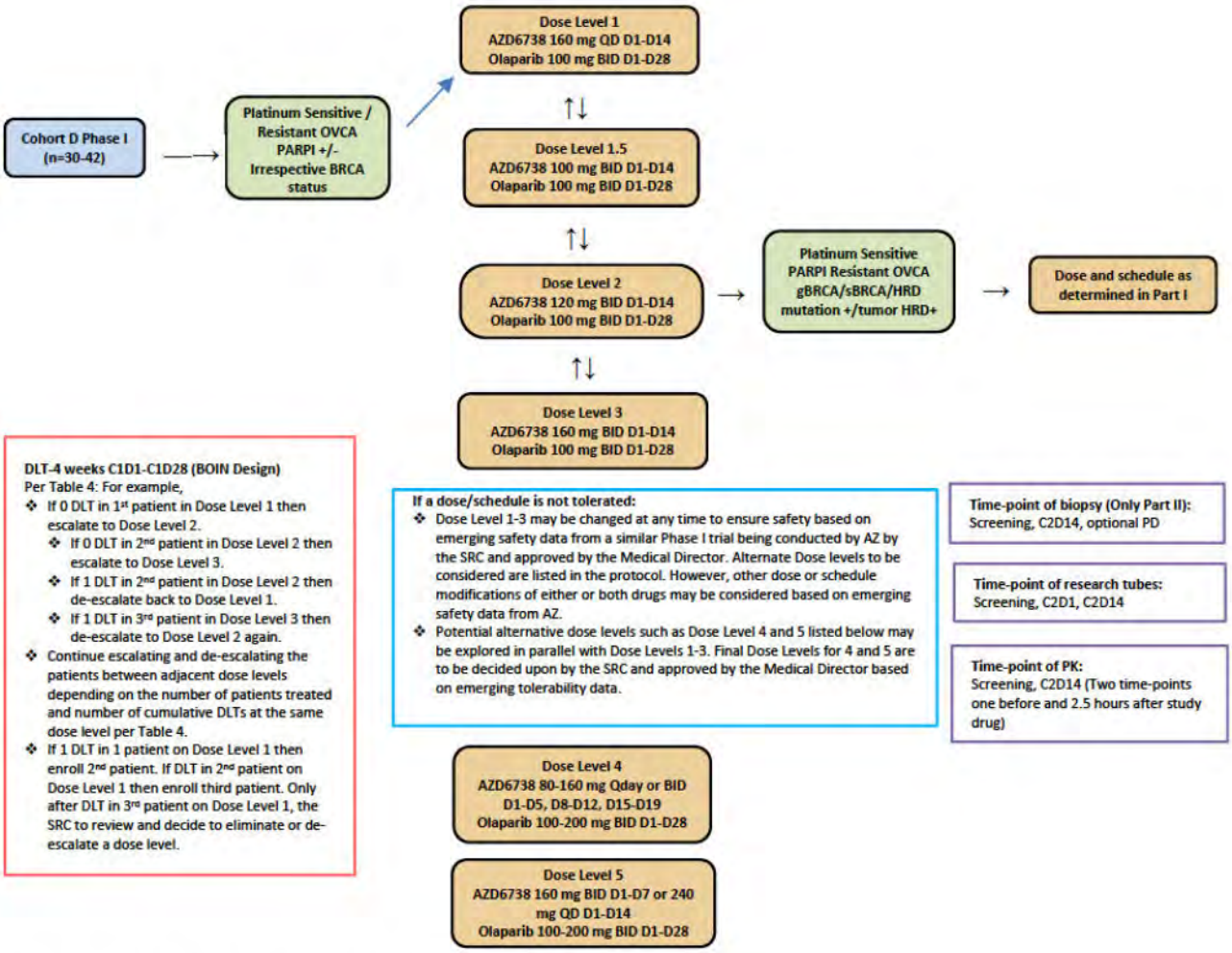
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Table 3. Indicative dose levels to explore in Cohort D Dose and Schedule Finding Part I

Dose Level	Dose of AZD6738	Dose of olaparib
1	160 mg QD Days 1-14	100 mg BID continuous
1.5	100 mg BID Days 1-14	100 mg BID continuous
2	120 mg BID Days 1-14	100 mg BID continuous
3	160 mg BID Days 1-14	100 mg BID continuous
Dose Level 1-3 may be changed at any time by the SRC with approval of the Medical Director to ensure safety based on emerging safety data from a similar Phase I trial being conducted by AZ. Alternate Dose levels for 1-3 to be considered are: AZD 6738 120 BID Day 1-10 and olaparib 100 BID D1-28; AZD6738 160 BID Day 1-Day 10 and olaparib 100 mg BID D1-28; AZD6738 140 mg BID D1-14 and olaparib D1-28; and olaparib 100 BID D1-28. Other dose or schedule modifications of either or both drugs may be considered and will **not exceed AZD6738 160 mg PO BID Days 1-14 and olaparib 150 mg PO BID** based on emerging safety data from AZ. Potential alternative dose level such as Dose level 4 and 5 listed below may be explored. Dose Level 4 or 5 may be tested in parallel while Dose Level 1, 2, or 3 are ongoing. Final Dose Levels 4 and 5 are to be decided upon by the Safety Review Committee with the approval of the Medical Director based on emerging tolerability data. **TO ENSURE SAFETY, THE PENN SITE WILL ASSIGN ALL SUBJECTS THEIR DOSE AND SCHEDULE FOR COHORT D.**		
4	80-160 mg QD or BID weekly intermittent schedule e.g. Days 1-5, 8-12, 15-19	100 to 200 mg BID continuous
5	160 BID Days 1-7 or 240 mg QD Days 1-14	100 to 200 mg BID continuous

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Figure 14. Cohort D Flow Chart



Conduct of Cohort D Part I (Dose and Schedule-finding)

The dose finding portion of Cohort D will implement the BOIN design to find the MTD (Liu and Yuan, Journal of the Royal Statistical Society: Series C 2015;64:507-23, 2015). The BOIN design can be implemented in a similar way as the traditional 3+3 but has been shown to have superior operating characteristics that comparable to model-based designs such as continual reassessment method (CRM). The dose escalation or de-escalation rules to evaluate the three proposed dose levels are provided in Table 4 and or the flow chart (Figure 15) (based on the observed DLT rate) below. The target DLT rate for the MTD for the current study is set at 30% and two alternatives; the highest DLT rate that deemed as sub-therapeutic is 25% and the lowest DLT rate that deemed as overly toxic is 35%. The 25% and 35% DLT rates were selected based on the prior Phase I experience with AZD6738 and olaparib (Study 4). Furthermore, to avoid assigning too many subjects to the overly toxic doses, a dose level will be eliminated when the posterior probability is greater than 95% that the toxicity rate of a dose level is >30% and if at least 3 subjects are treated at the dose level. Dose escalation will continue to enroll and treat subjects until a maximum of 12

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subjects are treated and evaluable for DLT at a given dose level or a maximum 30 subjects from all dose levels treated. The maximum number of subjects for a given dose level was selected to be 12 based on the recommendation of the BOIN design so that the trial can be stopped and select the MTD early if the dose finding portion are converged. We will escalate or de-escalate to the adjacent dose level (no skip dose) depending on how many cumulative DLTs (or DLT rate) out of total number treated in current dose level after each DLT evaluation. The starting dose level will be dose level 1. For the first three subjects, dose escalation or de-escalation will take place after treating one subject at a time with 28 days DLT period between each subject. If a DLT is observed in the first subject under dose level 1, we will continue to treat at dose level 1 until either dose level 1 is eliminated for overly toxic or we are able to escalate to the next dose level. The remaining does escalation or de-escalation will be done in a cohort of 3 subjects at a time without staggering between subjects. It is required to wait a 28-day period to assess for DLTs after a cohort of 3 patients are enrolled to a dose level for Dose Level 1-3 before the allocation to the next cohort of 3 patients is determined. The SRC, with Medical Director concurrence, may decide at any time to treat subjects sequentially with 28-day staggering for DLT assessment if additional safety issues arise. If dose level 1 is determined to be too toxic, the Safety Review Committee (SRC) will meet and discuss alternative doses for further exploration. The total number of subjects to be enrolled during the dose escalation part (Part I) will vary depending on the underling-dose-toxicity relationships and the number of doses tested before determining MTD. Cohort D Part II expansion phase will be followed after a dose is deemed MTD at the end of Part I. If none of the three (3) dose levels explored are tolerable or if the MTD identified is lower than the highest dose level explored, we will discuss with SRC to explore other alternative dosing schedules (e.g., Level 4, and level 5) using remaining subjects from the original 30 maximum number of subjects allocated to Cohort D Part I. Regarding enrollment to Alternate Dose Level 4 or 5, this may occur in parallel to enrollment of Dose Level 1-3 since this is evaluating two different dose schedules. Enrollment to Dose Level 4 or 5 will not use the BOIN design. For Dose level 4 or 5, three patients may be enrolled at a time. A 28 day DLT period will follow after 3 patients are enrolled prior to enrollment of additional patients. We may treat 3 to 6 patients to each Dose Level 4 and Dose Level 5 starting with Dose Level 4. We will start with a cohort of 3 patients, and if 0/3 and 1/3 patients incur a DLT, we will add 3 more patients. If 2/3 patients have a DLT, we will then then stop and determine that Dose Level intolerable. An alternative dose level may be proposed by the SRC. The SRC will review the data from all of the subjects recruited across dose cohorts and from emerging AZ trial data and may make changes to dose level as well as decide when to begin Cohort D Part II Expansion Phase in PARPi-resistant ovarian cancer patients. Medical Director approval is needed for changes to dose levels as recommended by the SRC.

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Table 4. Dose escalation or de-escalation for the proposed BOIN design

ESCALATION/DE-ESCALATION RULE											
Number of patients treated at current dose level											
1	2	3	4	5	6	7	8	9	10	11	12
Escalate to the next higher dose level if # of DLT <=											
0	0	0	1	1	1	1	2	2	2	3	3
De-escalate to the next lower dose level if # of DLT >=											
1	1	1	2	2	2	3	3	3	4	4	4
Eliminate this dose level if # of DLT >=											
NA	NA	3	3	4	4	5	5	5	6	6	7

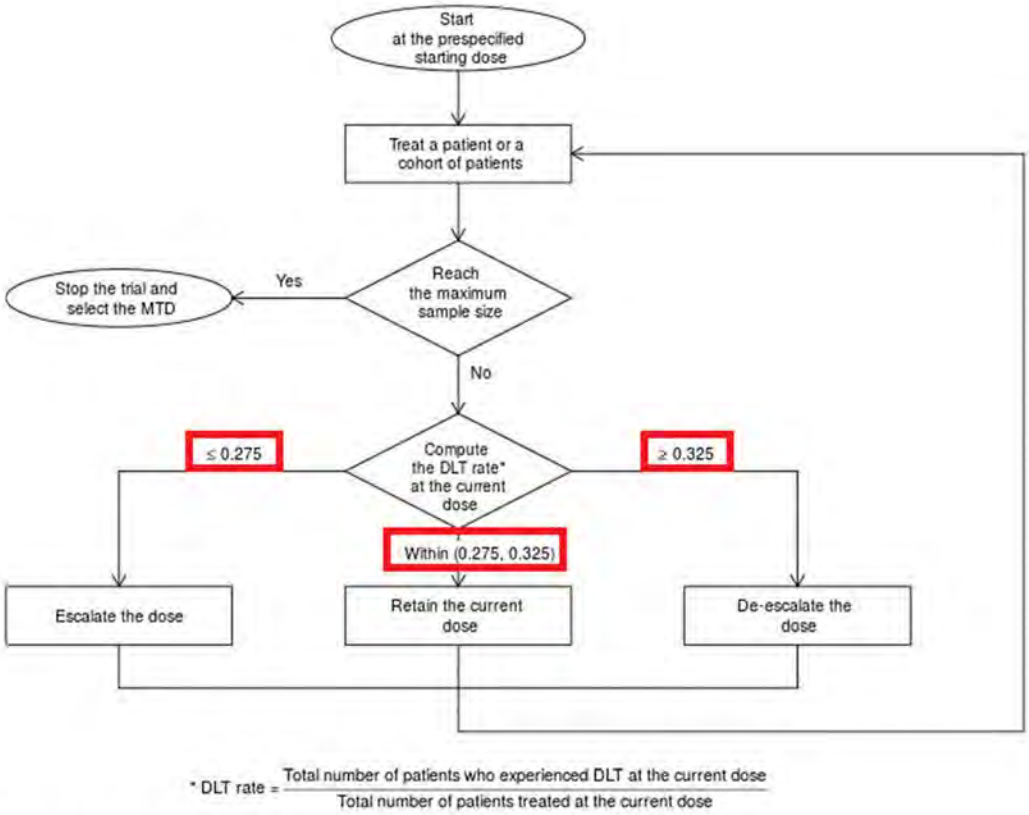


Figure 15. BOIN flow chart

That is, we escalate if the current observed DLT rate is ≤23.6%, stay in the current dose if the current observed DLT rate within 23.6% and 35.9% and de-escalate if the current observed DLT rate≥35.9%.

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Definition of DLT

A DLT is defined as any toxicity during the period of Cycle 1 (i.e., from dosing on Cycle 1, Day 1 until the last day of dosing in Cycle 1), which includes:

1. Hematological toxicities as follows:
   - Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting longer than 4 consecutive days
   - Grade 3 neutropenia (ANC ≥500 to <1000 cells/mm^3) of any duration accompanied by fever ≥ 38.5°C and/or systemic infection
   - Grade 3 thrombocytopenia (25,000 to <50,000/mm^3) with bleeding
   - Any other confirmed hematological toxicity ≥ CTCAE v 5.0 Grade 4 (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e. a suspected spurious value)
2. Non-hematological toxicity ≥ CTCAE 5.0 Grade 3 including:
   - Laboratory abnormalities (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e. a suspected spurious value)
   - QTc prolongation (> 500 msec)
3. Any other toxicity that is greater than that at baseline, and is clinically significant and/or unacceptable, and does not respond to supportive care
4. Any event, including significant dose reductions or omissions, judged to be a DLT by the SRC

A DLT excludes:

- Alopecia of any grade
- Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all patients should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment)
- Any toxicity clearly unrelated to AZD6738/olaparib combination e.g. solely related to the disease or disease-related process under investigation.

Definition of evaluable patient

For decisions on dose escalation, an evaluable patient is defined as a patient that has received AZD6738 and either:

- Has completed minimum safety evaluation requirements and has received at least 75% of the specified dose of AZD6738 during Cycle 1, and at least 75% of the specified dose of olaparib Cycle 1; or
- A patient will be evaluable for tumor assessment if they have at least one (1) measurable lesion at baseline.

Safety Review Committee

Once there are one (1) to three (3) evaluable patients at a dose level during the dose escalation phase of the study, a SRC will evaluate the safety and tolerability and, where available, pharmacokinetics of AZD6738 to decide the next dose and/or schedule. Any dose interruptions and reductions will be taken into account.

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The SRC will consist of:

- Principal Investigator or delegate, who will chair the committee, or delegate
- Medical Director (or Substitute)
- AstraZeneca Physician
- Investigator or delegate from other investigational sites
- In addition, one other physician or medical scientist from the following may be invited: AstraZeneca Global Safety Physician or delegate, AstraZeneca Medical Scientist from AZD6738 project, AstraZeneca physician from another project.

The AstraZeneca Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

The AstraZeneca Clinical Pharmacology Scientist, Study Statistician, Patient Safety Scientist, Study Leader, and other AstraZeneca and non-AstraZeneca technical experts may also be invited as appropriate. The Safety Review Committee Remit document for this study will define the exact membership and who should be present for decisions to be made. Further, AstraZeneca or non-AstraZeneca experts may be consulted by the SRC as necessary.

SRC decisions may be to:

- Proceed with dose escalation – refer to Section 4.2
- Expand the cohort to a maximum of 6 evaluable patients
- De-escalate the dose of AZD6738 either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
- Stop the dose escalation part of a study module
- Adjust the dosing frequency/schedule/sequence of AZD6738, with or without a concurrent change in dose
- Adjust the dose/dosing frequency/schedule(s)/sequence(s) of the combination agent(s)
- Stop this part of the study

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable. Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case-by-case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the Investigators prior to dosing any new patients.

See SRC document for further information in Appendix F. Safety Review Committee.

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Conduct of the Cohort D Part II Expansion Phase using the alternate AZD6738 and olaparib schedule

Once the SRC decides that a safe and tolerated alternate schedule is identified, Cohort D, Phase II may open to recruitment, enrolling patients with ovarian cancer who are PARP inhibitor (PARPi) resistant (patients who have progressed on a PARPi). Patients must be platinum sensitive and have a germline or somatic BRCA mutation or an HRD mutation. Other HRD mutations will be reviewed by the SRC or overall PI. A total of 12 additional subjects will be treated in this part.

We expect Cohort C to have completed enrollment by the time Cohort D, Part II is open for enrollment. However, if Cohort C has not completed enrollment, subjects will be assigned alternating between Cohorts C and D.

Safety and toxicity evaluation will proceed as follows: patients will be evaluated with history and physical, including blood pressure and weight, at Cycle 1, Day 1(±3 days), Cycle 1, Day 8 (±3 days), Cycle 1, Day 15 (± 3 days) and then Day 1 of each subsequent cycle (± 3 days for all visits starting on Cycle 2, Day 1 (See Figure 14; Table 6.). Triplicate EKGs will be required at baseline (i.e. within 28 days of enrollment). Safety evaluation will be performed prior to every clinic visit using CTCAE 5.0 and will also include documentation of concomitant medications including blood transfusions.

Response evaluation will proceed as follows: imaging studies will be performed initially after every two cycles (i.e. starting Cycle 3). If stable disease or response to therapy is documented after Cycle 4, imaging can then continue every three (3) cycles thereafter. Imaging can be done at a shorter interval per provider discretion. Response will be documented using RECIST 1.1 criteria. A confirmatory assessment of response (PR or CR) will occur 4 to 8 weeks after initial documentation of CR or PR (as per RECIST 1.1). The preferred imaging modality will be CT scan of the chest, abdomen, and pelvis with oral and intravenous contrast. Alternatively, after consultation with the study PI, MRI may be considered. MRI A/P with and without gadolinium and a CT of the chest without contrast will be performed if a patient is allergic to iodine. Imaging studies not covered by the patient's insurance as standard of care, will be covered by the study's financial sponsor.

Laboratory studies will be performed at screening, Cycle 1 at Day 1, Day 8 (±3 days) and Day 15 (±3 days) and at the start of each cycle thereafter, and as needed for safety measures. On Day 1, lab work will be required within three (3) days prior to the start of each cycle. Laboratory studies will include hematology, blood chemistries, and urinalysis (urine dipstick is only required at screening). CA-125 will be assessed as a part of screening and at the start of each cycle per standard of care. Coagulation parameters (PT, INR, PTT) will be assessed at enrollment and then as clinically indicated. Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Additional laboratory studies will be performed as clinically indicated.

Research Tumor Biopsy of a **non-target lesion** will be obtained only if they are safe and feasible of patients in Cohorts A, B, C, D PART II. Cohort D Part I dose and schedule finding will not require biopsies.

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For Cohort A-C, biopsy will occur prior to study drug initiation, at Cycle 2 Day 7 (if necessary, this can occur on Day 6 or 5, however Day 7 is ideal).

For Cohort D, PART I, Dose Level 4, biopsy, if done, will occur at Cycle 2, Day 12 (if necessary, can occur on day 11 or 13, but ideally on Day 12).

For **Cohort D, PART II, biopsy will occur prior to study drug initiation, at Cycle 2 Day 14** (if necessary, can occur on Day 13 or 15, but ideally on Day 14). **Biopsy at disease progression is encouraged but optional**. Please see below for blood studies that are to be obtained approximately at the same time of biopsy.

The Cycle 2 biopsy should occur 2.5 hours after study drug dosing; however, there is a window of 2.5 hrs ± 1 hour after patient takes study drug. It is preferred that biopsy is performed at least 2.5 hrs after study drug is taken and not before if possible. If a patient is deemed a candidate for biopsy, but the procedure is unsuccessful, the patient may still enroll onto the trial.

Surgical intervention (e.g. laparoscopy or laparotomy) will not be performed solely in order to obtain tissue but if clinically indicated. Biopsies will utilize an approach deemed most feasible and appropriate by the investigator, such as under radiology image guidance or surgical office biopsy. Biopsies from a new lesion or site of progression will be encouraged but optional at the time of drug discontinuation (if deemed safe and feasible). If progression of disease occurs in the setting of a surgical emergency (e.g. bowel obstruction or brain metastasis), discontinuation biopsy may be obtained during the otherwise indicated surgical intervention. The biopsy specimen when performed by radiology will consist of **5 needle core biopsies** which will be used for: i) formalin for paraffin embedding with H&E (one sample), (ii/iii) OCT (2 samples), iv) media and DMSO for PDX, and v) for organoid development. Instructions for processing should be followed using provided SOPs. When performed in the office or at time of otherwise indicated surgical procedures 1 cm^3 of tissue will be obtained and similarly processed. Archived patient tumor (e.g. from prior surgery or biopsy) may be obtained and evaluated for genomic or proteomic studies if available.

BLOOD SAMPLES will be collected for Research Studies (cfDNA, PBMC) and Pharmacokinetics.

BLOOD FOR RESEARCH STUDIES:

For **COHORT A-C, Blood (4 purple tops ~40ml) for Research Studies will be collected at 4 time points: (1) prior to beginning study treatment (on the same day of tumor biopsy), (2)** at **Cycle 2 Day 1** prior to drug dosing (can occur minus 1 or 2 days for example Cycle 1 Day 27 or 28 but Cycle 2 Day 1 is ideal), **(3)** at **Cycle 2 DAY 7** (if necessary, this can occur on Day 6 or 5, however Day 7 is ideal) **on SAME DAY of TUMOR BIOPSY and PK studies.** Ideally, blood samples are obtained at time close to when biopsy is obtained**.** Blood will be obtained **2.5 hours after study drug dosing** (same timing as peak PK blood draw). There is a window of 2.5 hrs ± 1 hour after am drug dosing of olaparib and AZD6738, **(4)** and **at Progression** as determined by RECIST (AM Lab draw). It is preferred that blood be obtained at least 2.5 hrs after study drug is taken and not before if possible.

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For **COHORT D: Blood (4 purple tops ~40ml) for Research Studies will be collected at 4 time points: (1) prior to beginning study treatment (on the same day of tumor biopsy), (2)** at **Cycle 2 Day 1** prior to drug dosing (can occur minus 1 or 2 days for example Cycle 1 Day 27 or 28 but Cycle 2 Day 1 is ideal), **(3)** at **Cycle 2 DAY 14 or the last day of theolaparib/AZD6738 combination during the second week of Cycle 2** (if necessary, this can occur minus 1 or 2 days, however the last combination day is ideal) **on SAME DAY of TUMOR BIOPSY and PK studies.** Ideally, blood samples are obtained at time close to when biopsy is obtained**.** Blood will be obtained **2.5 hours after study drug dosing** (same timing as peak PK blood draw). There is a window of 2.5 hrs ± 1 hour after am drug dosing of olaparib and AZD6738, **(4)** and **after Progression** as determined by RECIST (AM Lab draw) **at the end of treatment visit**. It is preferred that blood be obtained at least 2.5 hrs after drug is taken and not before if possible.

BLOOD FOR PHARMACOKINETIC STUDIES:

For Cohorts A and B, blood for PK (1 purple top ~ 7-9 ml) will be collected from the first 10 patients for each cohort. PK studies are not required for Cohort C. Blood will be processed for plasma and stored for plasma drug concentration PK analysis at the University of Pennsylvania to be possibly analyzed at a later time point. **Blood (1 purple top with ~ 7-9 ml) will be collected at 2 time points: (1) at screening, and (2) at Cycle 2, Day 7** same day as biopsy and research blood collection (if necessary, this can occur on Day 6 or 5, however Day 7 is ideal) Blood should be collected on **Cycle 2, Day 7 at 2 time-points**: **in the morning, just prior to the first dose of both study drugs (drug trough) and 2.5 hours ± 1 hour after the first dose of both drugs (drug peak)** and then stored in the Simpkins laboratory. Bio analysis to measure AZD6738 and olaparib (and potentially their metabolites) will be performed at a later time if determined necessary.

All patients in Cohort D Part I and Part II will have PK studies obtained. **Blood (1 purple top with ~ 7-9 ml) will be collected at 2 time points: (1) at screening, and (2) at Cycle 2, Day 14, or the last day of the olaparib/AZD6738 combination during the second week of Cycle 2** same day as biopsy and research blood collection (if necessary, this can occur minus 1 or 2 days, however the last combination day is ideal) Blood should be collected here at **Cycle 2, Day 14 (or the last olaparib/AZD6738 combination day of the second week of Cycle 2) at 2 time-points**: **in the morning, just prior to the first dose of both study drugs (drug trough) and 2.5 hours ± 1 hour after the first dose of both drugs (drug peak)** processed on site and then shipped to the Simpkins laboratory. Bio-analysis to measure AZD6738 and olaparib (and potentially their metabolites) will be performed at a later time if determined necessary.

Additional fluid samples for research (supernatant and pellet) may be collected for HRD, BRCA1/2, ATR pathway biomarkers, PARP1 expression, and other assays as feasible.

Study treatment will be continued until disease progression or lack of clinical benefit as determined by investigator, intolerable toxicity, or until a condition for discontinuation is met as in Section 6.8 Standard of care includes clinic visits, labs prior to every cycle, and imaging studies. Tumor biopsies, blood collection for research studies and PK are not standard of care and will be paid for by the study's financial sponsor. Trial related studies not covered by insurance will be covered by the study's financial sponsor.

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Patients participating in the FTT PARPi imaging tracer study will be at the University of Pennsylvania ONLY. Patients screening for CAPRI have the option to consent to the FTT PARP inhibitor imaging tracer study (IRB Protocol 823234). Patients will undergo PARPi tracer (18F-fluorthanatrace (FTT) imaging before starting any treatment, and on approximately day 5-7 after starting single agent olaparib (olaparib lead-in). Second FTT scan is optional but preferred. If patients are unable to do the second FTT scan, an olaparib lead-in is not required. Patients ideally will have a 7-day lead in of olaparib 300 mg BID daily prior to starting the combination of AZD6738 and olaparib. If necessary, this lead-in period can be shortened to 6 or 5 days, however 7 days is ideal. The olaparib will be dispensed through the CAPRI study. For patients enrolled on both Capri and FTT, the FTT study acts as a sub-study to CAPRI. A maximum of 30 CAPRI patients per cohort can be enrolled in the FTT study.

The 28-day screening period for CAPRI ends on Day 1 of the olaparib FTT lead-in. The baseline CT scan for CAPRI must be completed prior to the start of olaparib. A CBC, CMP, and provider visit must be completed within 3 days prior to administration of olaparib and all blood parameters must fall within the inclusion criteria of CAPRI to initiate treatment.

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Table 5. Study Schedule Cohorts A, B, and C

Cohort A, B, C											
Test	**Screening (≤28 Days)**	**Pre-Combination Olaparib Lead-in (Days 1-7)**	**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycle X[1]**	**EOT**	**FU[13]**
			D1 (±3 days)	**D 8 (±3 days)**	**D15 (±3 days)**	**D1**	**D7 (-2 days)**	**D1**	**D1**		
Eligibility Criteria	X										
Informed Consent	X										
Tumor Assessment (Imaging)[2]	X							X[4]		X	X
H&P	X		X	X	X	X^		X^	X^	X	X
ECOG	X		X	X	X	X^		X^	X^	X	X
EKG	X[3]										
Weight & Blood pressure	X		X	X	X	X^		X^	X^	X	X
Safety evaluation			X	X	X	X^		X^	X^	X	X
Laboratory											
CBC + Diff	X	X	X*	X	X	X*		X*	X*	X	
Blood Chemistries[6]	X		X*	X	X	X*		X*	X*	X	
Urinalysis (dipstick)	X										
CA-125	X		X*			X*		X*	X*	X	X
PT/PTT/INR	X[7]										
BRCA testing	X[12]										
Paracentesis if needed	X[11]										
Research											
Blood for research	X[8]					X[8]	X[8]			X[8]	
Plasma for PK	X[9]	X[10]					X[9]				
Biopsy[5]	X						X[5]			X[5]	
Treatment											
AZD6738[14]			D1 - D7			D1 - D7		D1 - D7	D1 - D7		
Olaparib		X[15]	D1 - D28			D1 - D28		D1 - D28	D1 - D28		
PARPi tracer Imaging											
FTT PET/CT[15]	X	X									

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* All tests marked with asterisk can be completed within 3 days prior to dosing
^ All tests marked with a caret sign can be completed within ±3 days of dosing
During holidays or planned vacations, visits and procedures including labs, may be done locally, virtually, or delayed beyond the 3-day window at the discretion of the site PI. If delayed beyond 7 days, sponsor approval is required. Biopsies however must be done in specified time and day windows as described previously.

Labs do not need to re-meet eligibility criteria on C1D1.

Days continue to count when study drug is held.

1. Repeat until Progression of Disease
2. The preferred imaging modality will be CT scan of the chest, abdomen and pelvis with oral and intravenous contrast. Alternatively, after consultation with the study site PI, MRI may be considered.
3. Triplicate EKGs 2 to 5 minutes apart will be done at screening and when clinically indicated
4. Imaging studies will be completed initially every two cycles. A confirmatory assessment of response (PR or CR) with repeat imaging will occur 4-8 weeks after initial documentation of CR or PR. If stable disease or response to therapy is documented after cycle 4, imaging can continue every 3 cycles thereafter. This assessment can occur within ±7 days of dosing
5. Cohorts A, B, C: will require all biopsies only if they are safe and feasible (Screening, On-Treatment, optional at PD). Patient's imaging will be reviewed in order to determine if the patient is a candidate for biopsy and has a minimum of 2 lesions. At least one lesion is needed for RECIST as a TARGET lesion to be followed for response and not undergo biopsy. A NON-TARGET lesion should be identified to be biopsied. If on day of biopsy, the predetermined Non-Target lesion is deemed not safe to biopsy it will be left up to the performing physician's discretion which lesion to biopsy based on patient safety. Biopsy of a NON-TARGET target lesion will be obtained prior to study drug initiation at screening period (< 28 days from signing consent), at Cycle 2, Day 7 (if necessary, this can occur on day 6 or 5, however day 7 is ideal) and at disease progression. The Cycle 2, Day 7 biopsy should occur 2.5 hours after study drug dosing, however there is a window of 2.5 hrs ± 1 hour after morning dose of olaparib and AZD6738. It is preferred that blood for PK on Cycle 2, Day 7 be obtained at least 2.5 hrs after drug is taken and not before if possible. Biopsy may be performed by interventional radiology or in the office setting (For example vaginal or skin metastasis). Five tissue samples will be obtained if possible. Biopsies from a new lesion or site of progression will be requested at the time of drug discontinuation.

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6. Blood chemistries include: sodium, potassium, calcium, magnesium, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, and albumin.
7. Performed at baseline and as clinically indicated
8. Blood samples for research including cell free DNA, peripheral blood mononuclear cells, and plasma will be collected at enrollment prior to treatment (on the same day of tumor biopsy), at Cycle 2 Day 1 (prior to drug dosing; can be ± 3 days)), at Cycle 2 Day 7 (if necessary, this can occur on Day 6 or 5, however Day 7 is ideal) on SAME DAY of TUMOR BIOPSY and PK studies. Blood will be obtained 2.5 hours after study drug dosing (same timing as PK blood draws), however there is a window of 2.5 hrs ± 1 hour after am drug dosing of olaparib and AZD6738, and at progression as determined by RECIST (AM Lab draw). It is preferred that blood be obtained at least 2.5 hrs after drug is taken and not before if possible.
9. For Cohorts A and B, the first 10 pts will have blood drawn for PK studies at UPenn. Blood for PKs will be collected after enrollment, at Cycle 2, Day 7 at 2 time points: once before and 2.5hrs after both study drug PARPi-ATRi. See Section 3.1 for windows that apply to these events.
10. At UPenn, optional extra PK studies are only for pts enrolled on FTT study. Pt will get blood collected just prior to FTT scan and after 1-21 days of olaparib lead in (see Section 3.1 for details on lead-in window), after am olaparib drug dose but just before second FTT scan (with routine nuclear medicine labs).
11. Research samples (supernatant and pellet) will be collected from patients who undergo either therapeutic or diagnostic thoracentesis or paracentesis while on study.
12. BRCA germline testing is standard of care and should be done on all patients and documented; status can be unknown prior to enrollment to Cohort A and B.
13. After completion of treatment, patients will f/u with their MD every 3-4 months as standard of care until progression or death.
14. AZD6738 needs to start on Day 1 with no +/-3 days
15. At UPenn, patients consenting to PARPi tracer study will receive a 7 lead in of olaparib 300 mg PO BID prior to starting combination. If necessary, this lead-in period can be shortened to 4,5, or 6 days; however, 7 days is ideal. FTT-PET/CT will be performed prior to starting any treatment. Optional post-therapy FTT PET/CT will occur 1-21 days after therapy initiation. Exceptions for timing of second FTT scan should be discussed with PI Post-therapy biopsy (if applicable) will occur 1-2 cycles after therapy initiation (e.g. CAPRI trial) or as clinically indicated. A third FTT PET/CT scan may be done at the time of suspected progression; this scan will be optional. Please see companion FTT protocol and ICF. Second FTT should be after olaparib am drug dose.

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Table 6. Study Schedule Cohort D

Cohort D											
Test	Screening (≤28 Days)	Pre-Combination Olaparib Lead-in (Days 1-7)	Cycle 1			Cycle 2		Cycle 3	Cycle X[1]	EOT	FU[13]
			D1 (±3 days)	D 8 (±3 days)	D 15 (±3 days)	D1	D14 (-2 days)	D1	D1		
Eligibility Criteria	X										
Informed Consent	X										
Tumor Assessment (Imaging)[2]	X							X[3*+]		X	X
H&P	X		X	X	X	X^		X^	X^	X	X
ECOG	X		X	X	X	X^		X^	X^	X	X
EKG	X[3]										
Weight & Blood pressure	X		X	X	X	X^		X^	X^	X	X
Safety evaluation			X	X	X	X^		X^	X^	X	X
Laboratory											
CBC + Diff	X	X	X*	X	X	X*		X*	X*	X	
Blood Chemistries[6]	X		X*	X	X	X*		X*	X*	X	
Urinalysis (dipstick)	X										
CA-125	X		X*			X*		X*	X*	X	X
PT/PTT/INR	X[7]										
BRCA testing	X[12]										
Paracentesis if needed	X[11]										
Research											
Blood for research	X[8]					X[8]	X[8]			X[8]	
Plasma for PK	X[9]	X[10]					X[9]				
Biopsy[5]	X						X[5]			X[5]	
Treatment											
AZD6738[14]			D1 - D14			D1 - D14		D1 - D14	D1 - D14		
Olaparib		X[15]	D1 - D28			D1 - D28		D1 - D28	D1 - D28		
PARPi tracer Imaging											
FTT PET/CT[15]	X	X									

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* All tests marked with asterisk can be completed within 3 days prior to dosing
^ All tests marked with a caret sign can be completed within ±3 days of dosing
During holidays or planned vacations, visits and procedures including labs, may be done locally, virtually, or delayed beyond the 3-day window at the discretion of the site PI. If delayed beyond 7 days, sponsor approval is required. Biopsies however must be done in specified time and day windows as described previously.

Labs do not need to re-meet eligibility criteria on C1D1.

Days continue to count when study drug is held.

1. Repeat until Progression of Disease.
2. The preferred imaging modality will be CT scan of the chest, abdomen and pelvis with oral and intravenous contrast. Alternatively, after consultation with the Site PI, MRI may be considered.
3. Triplicate EKGs 2 to 5 minutes apart will be done at screening and when clinically indicated
4. Imaging studies will be completed initially every two cycles. A confirmatory assessment of response (PR or CR) with repeat imaging will occur 4-8 weeks after initial documentation of CR or PR. If stable disease or response to therapy is documented after cycle 4, imaging can continue every 3 cycles thereafter. (i.e. Screening, Cycle 3, Cycle 5 and then Cycle 8, Cycle 11 etc.) This assessment can occur within ±7 days of dosing.
5. Cohort D: will require biopsies only if they are safe and feasible (Screening, On-Treatment, optional at PD). Cohort D patients will require biopsies (if safe and amenable). Subject's imaging will be reviewed in order to determine if the subject is a candidate for biopsy and has a minimum of 2 lesions. At least one lesion is needed for RECIST as a TARGET lesion to be followed for response and not undergo biopsy. A NON-TARGET lesion should be identified to be biopsied. If on day of biopsy, the predetermined Non-Target lesion is deemed not safe to biopsy it will be left up to the performing physician's discretion which lesion to biopsy based on subject safety. Biopsy of a NON-TARGET target lesion will be obtained prior to study drug initiation at screening period (≤ 28 days from signing consent), at Cycle 2 Day 14 (if necessary, this can occur on Day 13 or 12, however Day 14 is ideal) and at disease progression (optional). The Cycle 2 Day 14 biopsy should occur 2.5 hours after study drug dosing, however there is a window of 2.5 hrs ± 1 hr after morning dose of olaparib and AZD6738. It is preferred that blood for PK on Cycle 2, Day 14 be obtained at least 2.5 hrs after drug is taken and not before if possible. Biopsy may be performed by interventional radiology or in the office setting (For example vaginal or skin metastasis). Five tissue samples will be obtained if possible. Biopsies from a new lesion or site of progression will be requested at the time of drug discontinuation.

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6. Blood chemistries include: sodium, potassium, calcium, magnesium, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, and albumin.
7. Performed at baseline and as clinically indicated.
8. Blood samples for research including cell free DNA, peripheral blood mononuclear cells, and plasma will be collected at enrollment prior to treatment (on the same day of tumor biopsy), at Cycle 2 Day 1 (prior to dosing; - 2 days permitted), at Cycle 2 Day 14 or the last day of the olaparib/AZD6738 combination of the second week of Cycle 2 (if necessary, this can occur minus 1 or 2 days, however the last combination day is ideal) on SAME DAY of TUMOR BIOPSY and PK studies. Blood will be obtained 2.5 hrs after study drug dosing (same timing as PK blood draws), however there is a window of 2.5 hrs ± 1 hr after am drug dosing of olaparib and AZD6738, and at progression as determined by RECIST (AM Lab draw).
9. PK STUDIES: Cohort D Part I and Part II, all subjects will require PK studies as indicated in the table. Blood for PKs will be collected after enrollment prior to treatment, at Cycle 2, Day 14 or the last day of the olaparib/AZD6738 combination for Cycle 2 (ideally the last study drug combination Day of Cycle 2 but can occur – 2 days) at 2 time points: once before and 2.5 hrs after both study drug PARPi-ATRi (PK studies should occur on same day as research blood and biopsy if performed).
10. At the University of Pennsylvania, optional extra PK studies are only for pts enrolled on FTT study. Subjects will get blood collected just prior to FTT scan after an olaparib lead in (see Section 4.1 for details on lead-in window), after am olaparib drug dose but just before second FTT scan (with routine nuclear medicine labs).
11. Research samples (supernatant and pellet) will be collected from subjects who undergo either therapeutic or diagnostic thoracentesis or paracentesis while on study.
12. BRCA germline testing is standard of care and should be done on all subjects and documented.
13. After completion of treatment, subjects will follow up with their doctor every 3-4 months as standard of care until progression or death.
14. AZD6738 needs to start on Day 1 with no +/-3 days
15. At the University of Pennsylvania (Only Cohort D Part II Dose Expansion), subjects consenting to PARPi tracer study-may receive a 7-day lead in of olaparib 300 mg PO BID prior to starting combination. If necessary, this lead-in period can be shortened to 4, 5, or 6 days; however, 7 days is ideal. FTT-PET/CT will be performed prior to starting any treatment. Optional post-therapy FTT PET/CT may occur 1-21 days after therapy initiation. Exceptions for timing of second FTT scan should be discussed with PI. A third FTT PET/CT scan may be done at the time of suspected progression; this scan will be optional. Please see companion FTT protocol and ICF. Second FTT should be after olaparib am drug dose.

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4.2 Rationale for study design, doses and control groups

A prior Phase I study has determined the dose limiting toxicities and optimal dose of the combination of olaparib and AZD6738. The next step is to determine whether there is sufficient clinical activity in patients with recurrent ovarian cancer to warrant future studies. In addition to investigating efficacy, this trial will closely monitor adverse events and biochemical markers of response.

4.3 End of Study Definition

A clinical trial is considered completed (End of Study) when participants are no longer being examined or the last participant's last study visit has occurred (including long term follow up visits or contacts). A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Study Schedules, Table 5. and Table 6.

5 PATIENT SELECTION CRITERIA

Patients will be enrolled from the offices of medical and gynecologic oncologists at each participating site. All recruiting sites are primary referrals centers in their region for patients with gynecologic cancers.

5.1 Inclusion criteria

For inclusion in the study, patients must fulfill the following criteria:

1. Patients $\geq$ 18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a life expectancy of at least 6 months.
3. For Cohorts A-C, and Cohort D, Part II, patients must have high grade serous ovarian, primary peritoneal, and/or fallopian tube cancer histologically or cytologically confirmed that is recurrent and for which standard curative measures do not exist or are no longer effective. For Cohort D, Part I, patients may have any non-mucinous epithelial ovarian cancer (including histology's such as clear cell, or endometrioid). Pathology must be reviewed internally at the University of Pennsylvania, Johns Hopkins University, or Harvard University prior to initiation of treatment.
4. All patients under consideration for Cohorts A, B, C, and D, must be willing to undergo mandatory tumor biopsies (non-target lesion). Patients should have at least one lesion (non-target) for biopsy. However, for patients in Cohorts A, B, C, and D, if patients are found to not have a safe lesion to biopsy by the radiology team, they may still be enrolled in the study and forego the biopsy. Patients who undergo attempted biopsies that are unsuccessful may still enroll and receive study drug.
5. All patients must have a measurable disease by RECIST v1.1.

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6. Germline BRCA mutation status:
    - Cohorts A and B: Patients with unknown BRCA status or negative BRCA germline mutation status will be permitted to enroll in the study. Patients with known BRCA germline mutations will be permitted to enroll up to a maximum of 10 subjects per cohort.
    - Cohort C and Cohort D Part II: All subjects must have either a germline or somatic BRCA mutation, or other HRD mutation, or tumor is HRD positive. Other HRD mutations will be reviewed for consideration for enrollment by SRC or University of Pennsylvania PI.
    - Cohort D Part I: Patients will be enrolled irrespective of BRCA status.
7. Adequate renal function, defined as measured creatinine clearance ≥ 51 ml/min.
8. Adequate hepatic function, defined as AST and ALT levels ≤ 2.5 X ULN (for subjects with liver metastases, AST or ALT ≤ 5 × ULN) and total bilirubin < 1.5 X ULN, absent Gilbert's disease.
9. Adequate bone marrow function, defined as absolute neutrophil count (ANC ≥ 1.5 X 10^9/L), platelet count ≥ 100 x 10^9/L, and hemoglobin ≥ 10 g/dL (in the absence of transfusion within 28 days prior to dosing).
10. Patients must be at least 2 weeks from previous therapy for their ovarian cancer (chemotherapy, hormonal therapy, and radiation therapy, or investigational agents; 6 weeks for mitomycin C) to initiate screening and 3 weeks from previous therapy to initiate treatment. Hormones for breast cancer management may be continued at the discretion of the provider.
11. Platinum-sensitive is defined as recurrence >6 months by RECIST 1.1 imaging from last platinum. Platinum-resistant is defined as recurrence ≤ 6 months by RECIST 1.1 imaging from last platinum regimen).
    - For Cohort A, there is no limit to number of prior regimens.
    - For Cohort B, patients may not have had more than 3 prior cytotoxic therapies since the development of platinum-resistance.
    - Patients for Cohort D, Part I (dose escalation), patients may be either platinum-sensitive with no limit on prior regimens. Platinum-resistant patients are eligible but they may not have received more than 3 prior cytotoxic therapies since development of platinum resistance.
    - Cohort C and Cohort D, Part II, patients must be platinum-sensitive BUT with no limit to number of prior cytotoxic therapies. These patients must demonstrate adequate bone marrow function as determined by the treating physician.
12. Prior treatment with a PARPi is permitted but not mandatory for Cohorts A and B and Cohort D Part I. Prior treatment with PARPi is mandatory for Cohort C and D Part II. If a patient has received a prior PARPi, then the patient must have demonstrated a clinical

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benefit of PARPi treatment by an initial response (by CA-125 or imaging) to PARPi treatment or clinical benefit from PARPi treatment as maintenance therapy followed by disease progression for enrollment onto Cohort C and D Part II. Clinical benefit for maintenance is defined as: a) prior maintenance with PARPi after 1st line chemotherapy of at least 12 months or b) prior maintenance with PARPi after >1 line of chemotherapy for minimum of 6 months. Subjects on Cohort A may have received treatment with PARPi, clinically benefitted, but not have progressed on a PARPi. This arm is to evaluate participants who have received prior PARPi (PARPi after PARPi).

- If the prior PARP inhibitor used was olaparib, it must have been tolerated without dose reduction for hematological toxicities. Olaparib must have been tolerated at a dose of 300mg twice daily for Arms A, B, & C, Olaparib must have been tolerated at a dose of 200 mg twice daily or higher for Arm D.

  For Cohort C and D Part II, *patients may not have received cytotoxic chemotherapy in the interval between PARPi monotherapy and enrollment.*

13. Patients who have had major surgery (as defined by the Site PI) must be fully recovered and ≥4 weeks post-operative prior to enrolling on study.
14. Patients must be able to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening, or otherwise altering the product formulation. They should not have gastrointestinal illnesses that would preclude the absorption of AZD6738 or olaparib, which are oral agents.
15. Postmenopausal defined as:
    - Amenorrhea for 1 year or more following cessation of exogenous hormonal treatments;
    - LH and FSH levels in post-menopausal range for women under 50;
    - Radiation induced oophorectomy with last menses >1 year ago;
    - Chemotherapy-induced menopause with >1 yr interval since last menses;
    - Surgical sterilization (bilateral oophorectomy or hysterectomy).
16. Able to understand and voluntarily sign a written informed consent, and are willing and able to adhere to the protocol requirements.
17. Patients with a history of brain metastases diagnosed greater than one year prior to study entry may be considered if they received sterilizing therapy to the CNS (resection or radiation) and have been CNS recurrence-free for the one-year period.

5.2 Exclusion criteria

1. Patients with known brain metastases diagnosed within one year will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

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2. Patients who have had prior AZD6738 or other cell cycle checkpoint inhibitors such as other ATM or ATR inhibitor, WEE-1 inhibitor, or CHK1 (or 1/2) inhibitors.
3. Patients with a serious cardiac condition, such as congestive heart failure; New York Heart Association Class III/IV heart disease; unstable angina pectoris; myocardial infarction within the last 3 months; valvulopathy that is severe, moderate, or deemed clinically significant; or arrhythmias that are symptomatic or require treatment. Resting EKG with QTc > 470 msec on two or more time points within a 24-hour period or family history of long QT syndrome.
4. Patients with a systolic blood pressure <90 mm Hg at two consecutive visits or recurrent symptomatic orthostatic hypotension.
5. Lack of recovery of prior adverse events due to prior cancer therapy to Grade ≤1 (NCI CTCAE v5.0; except alopecia). Stable persistent Grade 2 peripheral neuropathy may be allowed as determined on a case-by-case basis at the discretion of the PI. Patients with platinum-related hypomagnesemia (on replacement) will be eligible.
6. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, clinically significant GI bleeding or hemoptysis within 28 days prior to the start of the study, or psychiatric illness/social situations that would limit compliance with study requirements.
7. Another previous, active or current invasive malignancy within the last five years, with the exception of curatively treated stage IA cervical carcinoma, or resected stage IA, Grade 1 endometrial cancer, noninvasive non-melanoma skin cancers, DCIS of the breast or other solid tumors including lymphomas (without bone marrow involvement). Patients with localized breast cancer who are disease free at least three years out from treatment may be eligible.
8. Immunocompromised patients or HIV-positive patients on HAART due to potential drug interaction.
9. Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is two weeks.
10. 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 olaparib is five weeks for enzalutamide or phenobarbital and three weeks for other agents.
11. Patients with myelodysplastic syndrome, acute myeloid leukemia, or with features suggestive of MDS/AML.
12. Major surgery within four weeks of starting study.
13. Patients with a known hypersensitivity to AZD6738 or olaparib or any of the excipients of the product.

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14. Platinum refractory (progress in first line platinum therapy) are excluded for Cohorts A, B, C, D PART II.
15. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within three weeks prior to study treatment.
16. Patients with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood and other body fluids.
17. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
18. Whole blood transfusions in the last 120 days prior to entry to the study.

6 STUDY CONDUCT

6.1 Restrictions during the study

6.1.1 Anti-cancer therapy

No other anti-cancer therapy is permitted during study participation.

6.1.2 Herbal supplements

Use of herbal supplements is not permitted during trial participation.

6.1.3 Exposure to sunlight

It is recommended to avoid excessive sun exposure while on AZD6738.

6.1.4 Grapefruit juice

For all patients, it is prohibited to consume grapefruit juice or Seville oranges (including marmalade, juice, etc.) while participating in the study.

6.2 Subject enrollment, randomization, and initiation of investigational product

Patients will be identified for screening from the clinical practice of medical and gynecologic oncologists at each participating institution and from amongst patients referred to these institutions specifically for clinical trial enrollment.

Once patients have been screened and confirmed eligible by the institution, subject enrollment data will be entered into the database (e.g. REDCap®). At this stage, availability of enrollment slots will be confirmed. All registration information (signed informed consent, HIPAA authorization, H&P, baseline laboratory studies, pathology slides and report, CT scan report, and BRCA testing results (when available) will be sent to the study coordinator and study site PI for review and eligibility confirmation. If determined eligible by site PI, registration information should be forwarded and reviewed by University of Pennsylvania PI (Dr. Simpkins) or University of Pennsylvania CO-I (Dr. Shah or Dr. Martin) to confirm eligibility and slot availability. Once reviewed, a slot will be marked for the subject and enrollment considered complete.

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This is an open label study. We expect Cohort C to complete enrollment prior to completion of Cohort D Part I. However, in the case Cohort C is still open to enrollment when Cohort D Part II is ready to enroll, patients will be alternatively assigned to Cohort C and D.

6.3 Procedures for handling subjects incorrectly enrolled or initiated on investigational product

If patients have incorrectly enrolled on trial, their participation will be immediately halted once identified. If this occurs prior to initiation of treatment, they will be withdrawn and replaced.

If a patient is incorrectly enrolled on trial, but this is not noted until after they have initiated therapy, the course of action will depend upon the number of cycles of treatment they have received and the response to treatment. The medical monitor will be consulted regarding all patients incorrectly enrolled on trial.

- If the patient has completed two cycles of treatment and imaging demonstrates RECIST criteria response to treatment, the patient will be permitted to continue on treatment until progression of disease or unacceptable toxicity occurs.
- If the patient has not completed two cycles of treatment, the decision will fall to the discretion of the Sponsor who will consider all relevant factors including number of doses completed and sequence that led to inappropriate enrollment.

6.4 Blinding and procedures for unblinding the study

6.4.1 Methods for ensuring blinding

Not applicable

6.4.2 Methods for unblinding the study

Not applicable

6.5 Treatments

6.5.1 Identity of investigational product(s)

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib and AZD6738 to the Sponsor per agreement. The olaparib will be supplied in tablet form.

Investigational product	Dosage form and strength
Olaparib	*150 mg tablet and 100 mg tablet*
AZD6738	*100, 80 & 20 mg tablets*

AZD6738 inactive ingredients are mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and silicon dioxide. The coating is Opadry® II.

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Olaparib inactive ingredients are copovidone, colloidal silicon dioxide, mannitol, and sodium stearyl fumarate. The tablet coating is comprised of hydroxypropyl methylcellulose, macrogol 400, titanium dioxide, iron oxide yellow and iron oxide black.

6.5.2 Doses and treatment regimens

Olaparib tablets and AZD6738 will be separately packed in high-density polyethylene (HDPE) bottles with child-resistant closures. A separate bottle will be dispensed to each patient to cover the 7 days of single agent olaparib. After that, each dosing container will contain sufficient study drug for 28 days plus overage. The study drug will be dispensed to patients prior to the start of each cycle until the patient completes or withdraws from the study, or progresses on study drug, or no longer derives clinical benefit from study drug.

Olaparib and AZD6738 may be stored at room temperature. The label on the bottle specifies the appropriate storage.

Patients will complete a log for each drug (drug diary) to track administration.

Cohorts A to C

Patients will be administered olaparib orally twice daily at 300 mg BID continuously. The tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food.

Patients will be administered AZD6738 orally once daily at 160 mg on days 1 to 7. The tablets should be taken at the same time each day (within two-hour window) and swallowed whole and not chewed, crushed, dissolved, or divided. For ease of administration, the AZD6738 should be administered at the same time as one of the olaparib doses and thus with one glass of water. When AZD6738 is administered in combination with olaparib, patients must fast as directed for at least two hours prior to the dosing and for at least one hour after the dose. When olaparib is given on its own, the olaparib tablet formulation can be given without regard to food.

Should any patient enrolled on the study miss a scheduled dose for any reason, the patient will be allowed to take the scheduled dose up to a maximum of two hours after the scheduled dose time. If greater than two hours after the scheduled dose time, the missed dose is not to be taken. The patient should take the next dose as scheduled.

If vomiting occurs shortly after the tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted.

Cohort D Part I and II

Patients will be administered study drug according to dosing schema for Cohort D.

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If the SRC decides upon different or additional cohorts, then sufficient numbers of tablets plus overage will be supplied. For once or twice-daily dosing AZD6738 should be taken at the same time as the morning and evening doses of olaparib. In this case, patients must fast as directed for at least two hours prior to the dosing and for at least one hour after the dose taken.

6.5.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling.

Each bottle 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
- Enrollment code (E-code)
- Date of dispensing
- Instructions stating that each dose should be taken at approximately the same time

6.5.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the Investigator's Brochure specifies the appropriate storage.

6.5.5 Management of toxicity

Guidelines for the management of hematological and non-hematological AEs for AZD6738 and olaparib are described below. Toxicity will be assessed utilizing the NCI Common Terminology Criteria for Adverse Event (CTCAE) version 5.0. Every effort should be made to administer trial treatment at the planned dose and schedule. However, patients experiencing toxicities related to the trial treatment may have their dose modified as outlined in this section.

A new cycle of AZD6738 and olaparib cannot begin unless the following criteria are met:

- ANC 1.0×10^9/L
- Platelets 75×10^9/L

In the event that they are not met, AZD6738 and olaparib dosing should be halted until ANC and platelet count are restored to within the acceptable criteria.

In the event that a patient has not recovered sufficiently to enable the next cycle to start, then the cycle should be delayed until the toxicity has recovered sufficiently to allow further dosage. The maximum cycle delay is permitted in 28 days. Any patient requiring a toxicity related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Medical Director for the patient to continue.

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If Day 1 treatment with either AZD6738 or olaparib is interrupted, then both study drugs will be delayed until the combination can be resumed. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. (A treatment delay for any Cycle, Day 1 means holding both drugs).

Study treatment can be dose reduced by first dose reduction as described in Section 6.5.6. Treatment must be interrupted if any CTCAE 5.0 Grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

Management of hematological toxicity

Table 7. Guidance for dose reductions for AZD6738 for hematological toxicity

Initial dose level	**1st dose reduction**	**2nd dose reduction**	**3rd dose reduction**
COHORT A-C			
160 mg QD Days 1-7	160mg QD Days 1-4	120 mg QD Days 1-4	None permitted; withdraw patient and treat as clinically indicated.
COHORT D			
160 mg BID Days 1-14	120 mg BID Days 1-14	160 mg QD Days 1-4	160 mg QD Days 1-7
120 mg BID Days 1-14	160 mg QD Days 1-14	120 mg QD Days 1-14	120 mg QD Days 1-7
160 mg QD Days 1-14	120 mg QD Days 1-14	120 mg QD Days 1-7	120 mg QD Days 1-4
Alternative Doses			
100 mg BID Days 1-14	100 mg PO BID Days 1-10	100 mg PO BID Days 1-7	100 mg PO QD Days 1-7
120 mg BID Days 1-10	160 mg QD Days 1-10	120 mg QD Days 1-10	120 mg QD Days 1-7
140 mg BID Days 1-14	140 mg BID Days 1-7	140 mg QD Days 1-7	140 mg QD Days 1-4
80 mg BID Days 1-5, 8-12, and 15-19	160 or 120 mg QD Days 1-5, 8-12, and 15-19. Discuss with study PI.	Discuss with study PI	Discuss with study PI

Dose must not be re-escalated even if toxicities have resolved in subsequent cycles.

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Table 8. Guidance for dose reductions for Olaparib for hematological toxicity

Initial dose level	1st dose reduction	2nd dose reduction	3rd dose reduction
COHORT A-C			
300 mg BID Days 1-28	250 mg BID Days 1-28	200 mg BID Days 1-28	None permitted; withdraw patient and treat as clinically indicated.
COHORT D			
150 mg BID Days 1-28	100 mg BID Days 1-28	None permitted; withdraw patient and treat as clinically indicated	N/A
100 mg BID Days 1-28	None permitted; withdraw patient and treat as clinically indicated	N/A	N/A

Dose must not be re-escalated even if toxicities have resolved in subsequent cycles.
N/A = Not Applicable

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Table 9. Anemia only

CTCAE 5.0 Grade	Investigations & Clinical management	Olaparib management	Dose of olaparib upon restarting	AZD6738 management	Dose of AZD6738 upon restarting
Grade 1 (Hgb < LLN – ≥ 10.0 g/dl)	None required	None required	N/A	None required	N/A
Grade 2* (Hgb < 10.0g/dl - ≥ 8 g/dl)	Investigator judgment to administer supportive therapy (e.g. transfusion)	None required Investigator discretion to transfuse or interrupt for maximum of 4 weeks until Hgb ≥8.	*First occurrence:* Resume at current dose. *Second occurrence:* investigator discretion whether to reduce by 1 dose level. *Third occurrence:* investigator discretion to reduce by 1 dose level	Investigator decision whether to interrupt AZD6738 and/or olaparib Investigator discretion to interrupt for maximum of 4 weeks.	*First occurrence:* Resume at current dose. *Second occurrence*: provider discretion whether to consider simultaneous reduction of AZD6738
Grade 3* (Hgb < 8 g/dl)	Repeat Hgb and reticulocyte count weekly until haemoglobin is improved to ≥ 8 g/dl	Hold treatment, repeat CBC + reticulocyte weekly Resume treatment when haemoglobin is improved to ≥ 8 g/dl	*First occurrence:* investigator discretion to reduce 1 dose level *Second occurrence:* recommend to reduce to one dose level	Hold treatment, repeat CBC + reticulocyte weekly Resume treatment when haemoglobin is improved to ≥ 8 g/dl	Investigator discretion to reduce by 1 level or resume at current dose *Second Occurrence:*

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CTCAE 5.0 Grade	Investigations & Clinical management	Olaparib management	Dose of olaparib upon restarting	AZD6738 management	Dose of AZD6738 upon restarting
	Administer supportive therapy (e.g. transfusion).		Third occurrence, reduce one additional dose level		At second occurrence reduce by 1 dose level Investigator discretion to consider simultaneous dose reduction in AZD6738
Grade 4* **(life-threatening consequences; urgent intervention indicated)**	Repeat Hgb and reticulocyte count weekly until haemoglobin is improved to ≥ 8 g/dl. Administer supportive therapy (e.g. transfusion).	Hold treatment, repeat CBC + reticulocyte weekly Resume treatment when haemoglobin is improved to ≥ 8 g/dl	*First occurrence:* reduce by 1 dose level *Second occurrence:* Discontinue study therapy	Hold treatment, repeat CBC + reticulocyte weekly Resume treatment when haemoglobin is improved to ≥ 8g/dl	*First occurrence:* reduce by 1 dose level *Second occurrence:* Investigator discretion whether to re-start at dose level -1 or stop.

*At the **first** occurrence of ≥Grade 2 anemia and thereafter at physician discretion, in addition to labs above, check peripheral blood smear and common treatable causes of anemia such as folate, B12, iron, transferrin, transferrin saturation, ferritin, haptoglobin, TSH.

For cases where patients develop prolonged hematological toxicity (≥4-week interruption/delay in study treatment due to CTCAE 5.0 Grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 6.5.5 for the management of this.

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Table 10. Neutropenia and/or leukopenia only

CTCAE 5.0 Grade	Olaparib management	Dose of olaparib upon restarting	AZD6738 management	Dose of AZD6738 upon restarting
Grade 1 (ANC <LLN - 1500/mm^3)	None required	No change required	None required	No change required
Grade 2 (ANC <1500/mm^3 – 1000/mm^3)		No change required	No change required	May dose reduce one dose level.
Grade 3 (ANC <1000 - 500/mm^3), uncomplicated or Grade 4	Hold treatment, repeat CBC + differential and reticulocyte weekly Resume treatment when improved to Grade 2 or better	First occurrence: May resume at current dose Second occurrence: reduce by 1 dose level Third occurrence: dose reduce by 1 additional level Fourth occurrence: discontinue study treatment	Hold treatment, repeat CBC + differential and reticulocyte weekly Resume treatment when improved to ≥1500/mm^3.	First occurrence: Dose reduce by 1 level **Subsequent occurrences:** Interrupt drug (max 28 days) and give appropriate supportive treatment. Investigator discretion whether to restart treatment with a reduced dose of AZD6738 and/or olaparib or to stop treatment.
Grade 3 (ANC <1000-500/mm^3) associated with a documented infection or temperature ≥38.3°C or ≥101°F	Hold treatment, repeat CBC + differential and reticulocyte weekly Resume treatment when improved to Grade 2or	First occurrence: Resume at current dose	Hold treatment, repeat CBC + differential and reticulocyte weekly.	First occurrence: reduce by 1 dose level Subsequent occurrences: dose reduce by 1 level

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CTCAE 5.0 Grade	Olaparib management	Dose of olaparib upon restarting	AZD6738 management	Dose of AZD6738 upon restarting
	better and infection resolved	Second occurrence: dose reduce by 1 level Third occurrence: discontinue study treatment	Resume treatment when improved to Grade 2 or better and infection resolved	Third occurrence: Reduce by 1 additional level Fourth occurrence: discontinue study treatment

If **repeat** occurrences of ≥Grade 2 neutropenia and thereafter at physician discretion, in addition to labs above, check peripheral blood smear.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended.

If a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to NCCN guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for PEGylated G-CSF) of the last dose of study treatment.

For cases where patients develop prolonged hematological toxicity (≥4 week interruption/delay in study treatment due to CTCAE 5.0 Grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section6.5.5 for the management of this.

Table 11. Thrombocytopenia only

CTCAE 5.0 Grade	Olaparib management	Dose of olaparib upon restarting	AZD6738 management	Dose of AZD6738 upon restarting
Grade 1 (platelets <LLN - ≥75,000)	None required	N/A	None required	N/A
Grade 2 and 3 (platelet count <75,000 - ≥50,000/mm^3 is grade 2;	Repeat CBC + differential and reticulocyte weekly until recovery to Grade 1	No change required	Repeat CBC + differential and reticulocyte weekly until recovery to at least ≥100,000/mm^3.	First occurrence: Resume at current dose. However, if blood counts do not recover by the start of the next dosing period, ceralasertib

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CTCAE 5.0 Grade	Olaparib management	Dose of olaparib upon restarting	AZD6738 management	Dose of AZD6738 upon restarting
<50,000 - ≥25,000/mm^3 is grade 3)			If on repeat labs platelets 50-75,000/mm3, dose interrupt (for a maximum of 4 weeks) until platelets resolve to at least ≥100,000/mm^3.	should be restarted with a dose reduction by 1 level for ceralasertib. **Subsequent occurrences** Interrupt ceralasertib only (max 28 days) and give appropriate supportive treatment. Treatment may be restarted with a reduced dose of ceralasertib when the toxicity is resolved or investigator discretion to stop treatment.

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CTCAE 5.0 Grade	Olaparib management	Dose of olaparib upon restarting	AZD6738 management	Dose of AZD6738 upon restarting
Grade 4 (platelet count <25,000/mm^3)	Hold treatment (for a maximum of 4 weeks), repeat CBC + differential and reticulocyte weekly Resume treatment when platelet count is improved to at least ≥100,000/mm3	Resume at current dose Second & subsequent occurrence: consider simultaneous AZD6738 and olaparib dose reductions	Repeat CBC + differential and reticulocyte weekly until recovery to at least ≥100,000/mm3≥100,000/mm3 If on repeat labs platelets 50-75,000/mm3, dose interrupt (for a maximum of 4 weeks) until platelets resolve to at least ≥100,000/mm3	First occurrence: re-start with dose reduced 1 level or stop treatment Subsequent occurrences: dose reduce by 1 additional level Third occurrence: dose reduce by 1 additional level Fourth occurrence: dose reduce by 1 additional level Fifth occurrence: No further dose reductions, discontinue study

At the **first** occurrence of ≥Grade 2 thrombocytopenia and thereafter at physician discretion, in addition to labs above, check peripheral blood smear.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged hematological toxicity (≥4 week interruption/delay in study treatment due to CTCAE 5.0 Grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 6.5.5for the management of this.

Please note that, for each dose reduction, the investigator may choose to reduce AZD6738 or olaparib or both drugs at their discretion, based on their attribution of relatedness. For example, if the adverse event is not thought to be related to olaparib,

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dose reduce AZD6738 only or both olaparib and AZD6738. If only one drug is dose reduced, the second drug may be reduced as an additional step. Refer to Table 14 for specific dose modification guidance regarding non-hematological toxicity.

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Multiple adverse hematologic toxicities*

If there are two hematological toxicities, treat according to the most conservative approach.

For cases where patients develop prolonged hematological toxicity (≥4 week interruption/delay in study treatment due to CTCAE 5.0 Grade 3 or worse anemia and/or development of blood transfusion dependence), refer to section 6.5.5 for the management of this.

Recommended dose-reductions will depend on the toxicity and are the following: If the hematologic toxicity is anemia, dose-reduce olaparib only; if the toxicity is thrombocytopenia and/or neutropenia, dose-reduce AZD6738 only (shorten number of days rather than reduce dose); if the toxicity is a combination of anemia with thrombocytopenia and/or neutropenia, dose-reduce both olaparib and AZD6738. If the adverse event is not thought to be related to olaparib, dose reduce AZD6738 or both olaparib and AZD6738. For a second dose-reduction, follow the guidance above on which of either, or both agents, to dose-reduce depending on the observed toxicity.

Management of prolonged hematological toxicities while on study treatment

Prolonged hematological toxicity is defined as:

- ≥4 week interruption/delay in study treatment due to CTC Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥4 week interruption/delay in study treatment due to CTC Grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥4 week interruption/delay in study treatment due to CTC Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

If a patient develops prolonged hematological toxicity, weekly blood counts including reticulocytes will be performed until resolution to Hgb ≥9g/dl. If any blood parameters remain clinically abnormal after four weeks of dose interruption, the patient should be referred to a hematologist for further investigations. Study treatment should be discontinued if blood counts do not recover to grade 1 or Hgb *≥10 g/dl* or better within 4 weeks of dose interruption. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. All patients who experience prolonged cytopenia ≥4 weeks should still undergo assessment for MDS/AML. Study treatment should be discontinued if a patient's diagnosis of MDS and/or AML is confirmed.

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 Sponsor to AstraZeneca Patient Safety.

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Management of non-hematological toxicity

Table 12. Guidance for dose reductions for AZD6738 for non-hematological toxicity

Initial dose level	1st dose reduction	2nd dose reduction	3rd dose reduction
COHORT A-C			
160 mg QD Days 1-7	120 mg QD Days 1-7	120 mg QD Days 1-4	None permitted; withdraw patient and treat as clinically indicated.
COHORT D			
160 mg BID Days 1-14	120 mg BID Days 1-14	160 mg QD Days 1-14	120 mg QD Days 1-14
120 mg PO BID Days 1-14	100 mg PO BID Days 1-14	160 mg QD Days 1-14	160 mg QD Days 1-7
160 mg QD Days 1-14	120 mg QD Days 1-14	120 mg QD Days 1-7	120 mg QD Days 1-4
160 mg QD Days 1-7	120 mg QD Days 1-7	120 mg QD Days 1-4	None permitted; withdraw patient and treat as clinically indicated.
Alternative Dosing Levels:			
100 mg BID Days 1-14	80 mg PO BID Days 1-14	120 mg PO QD Days 1-14	120 mg PO QD Days 1-7
120 mg BID Days 1-10	100 mg BID Days 1-10	120 mg QD Days 1-10	120 mg QD Days 1-4
160 mg BID Days 1-10	AZD 120 mg BID Days 1-10	160 mg QD Days 1-10	160 mg QD Days 1-7
140 mg BID Days 1-14	120 mg BID Days 1-14	160 mg QD Days 1-14	160 mg QD Days 1-7
80 mg BID Days 1-5, 8-12, 15-19	160 or 120 mg QD Days 1-5, 8-12, and 15-19. Discuss with study PI.	Discuss with study PI	Discuss with study PI

Dose must not be re-escalated even if toxicities have resolved in subsequent cycles.

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Table 13. Guidance for dose reductions of Olaparib for non-hematological toxicity

Initial dose level	1st dose reduction	2nd dose reduction	3rd dose reduction
COHORT A-C			
300 mg BID Days 1-28	250 mg BID Days 1-28	200 mg BID Days 1-28	None permitted; withdraw patient and treat as clinically indicated.
COHORT D			
150 mg BID Days 1-28	100 mg BID Days 1-28	None permitted; withdraw patient and treat as clinically indicated	N/A
100 mg BID Days 1-28	None permitted; withdraw patient and treat as clinically indicated	N/A	N/A

Dose must not be re-escalated even if toxicities have resolved in subsequent cycles.

N/A = Not Applicable

Please note that, for each dose reduction, the investigator may choose to reduce AZD6738 or olaparib or both drugs. ***If the adverse event is not thought to be related to olaparib, dose reduce AZD6738 or both olaparib and AZD6738***. If only one drug is dose reduced, the second drug may be reduced as an additional step. Refer to Table 14 for specific dose modification guidance regarding non-hematological toxicity.

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Table 14. Guidance on the management of Grade ≥ 3 non-hematologic toxicities for AZD6783 and olaparib

Occurrence	AZD6738 and olaparib
1st occurrence	Withhold dose and monitor at least weekly for up to 28 days until recovery to ≤CTCAE v5.0 Grade 1 then resume at original dose level. If a clinical CTCAE v5.0 give supportive measures and rule out other causes; if a laboratory AE is not resolving within two weeks contact Sponsor for guidance. If symptoms do not recover to ≤CTCAE v5.0 Grade 1, contact Sponsor and consider discontinue AZD6738 and olaparib.
2nd occurrence	Withhold dose for up to 28 days until recovery to ≤CTCAE v5.0 Grade 1 then resume at 1st dose-reduced level. If symptoms do not recover to ≤CTCAE v5.0 Grade 1, contact Sponsor and consider discontinue AZD6738 and olaparib.
3rd occurrence	Withhold dose for up to 28 days until recovery to ≤CTCAE v5.0 grade 1 then resume at 2nd dose-reduced level. If symptoms do not recover to ≤CTCAE v5.0 Grade 1, contact Sponsor and consider discontinue AZD6738 and olaparib.
4th occurrence	Discontinue study participation

Management of renal impairment

If subsequent to study entry and while still on study therapy, a subject's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly. When clinically appropriate, reversible etiologies of renal impairment should be excluded (e.g. dehydration, obstruction, other medication toxicity (e.g. Ibuprofen)). If GFR remains stable within 10% of the first value of GFR <51, subject may continue at present dose and provider will follow GFR closely with monthly labs. If olaparib dose was reduced, (e.g. because GFR continued to decrease after weekly testing), but GFR remains <51 and stabilizes, subject may continue olaparib at the current dose.

In subjects who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31-50 ml/min), the recommended dose reduction of olaparib is to 200 mg (two 100 mg tablets) twice daily, for a total daily dose of 400 mg.

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Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease. If subjects develop severe impairment or end stage disease it is recommended that olaparib be discontinued.

Management of hepatic impairment

No dose adjustment is recommended for mild hepatic impairment. For subjects with moderate or severe hepatic impairment therapy will be discontinued.

Drugs should be stopped if:

- ALT or AST or ALP* > 5 × ULN
- ALT or AST or ALP* > 3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (>5%)

  [ALT or AST > 3 × ULN] and [total bilirubin > 2 × ULN or INR+ >1.5 (unless patient is receiving warfarin) or other evidence of impairment to the synthesis function of the liver]

  *In the presence of bone metastasis, assess bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver).

Please refer to Appendix A. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law").

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination: signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2: saturation of peripheral oxygen (SpO2).
- Other items: when pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:

  (i) ILD markers (KL-6, SP-D) and β-D-glucan

  (ii) Tumour markers: Particular tumour markers that are related to disease progression.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

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Management of gastrointestinal toxicity

Events of nausea and vomiting are known to be associated with olaparib and AZD6738 treatment. These events are generally mild to moderate (CTCAE 5.0 Grade 1 or 2) severity, intermittent, and manageable on continued treatment.

If vomiting occurs shortly after the tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should a patient enrolled on the study miss a scheduled dose for any reason, the patient will be allowed to take the scheduled dose up to a maximum of two hours after the scheduled dose time. If greater than two hours after the scheduled dose time, the missed dose is not to be taken. The patient should take the next dose as scheduled.

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. Alternatively, olaparib can be taken with a snack (i.e. two pieces of toast or a couple of biscuits/cookies.

Toxicity management in Cohort D

If at any point during study treatment, it becomes apparent that the tumor is not coming under control, patients are to be removed from study and treated as clinically indicated.

If a patient experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted, or the dose reduced, and supportive therapy administered as required. If the toxicity resolves or reverts to ≤ CTCAE 5.0 Grade 2 treatment with AZD6738 may be restarted using the rules below for dose modifications only following agreement with the Principal Investigator.

For all other events, if the toxicity does not resolve to ≤ CTCAE 5.0 Grade 2 or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity. In the case of a fall in lymphocytes to CTCAE 5.0 Grade 2 or higher, the Investigators will be advised to perform an assessment of the lymphocyte populations. Patients may continue to receive AZD6738 as long as they are continuing to receive olaparib and in the absence of discontinuation criteria.

Treatment with AZD6738 should continue to the existing schedule subject to the following criteria being met. In the event that they are not met, AZD6738 dosing should be halted until ANC and platelet count are restored to within the acceptable criteria:

- ANC $\geq 1.0 \times 10^9$ /L
- Platelets $\geq 100 \times 10^9$ /L

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. The maximum duration of any dose interruption is 28 days. Treatment must be interrupted until the patient recovers completely or the toxicity reverts to Hg 9 (Grade 2) for anemia only, or to the baseline CTCAE 5.0 grade. If the interruption is any longer, the study team must be informed.

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At the first occurrence of CTCAE 5.0 Grade 3 and 4 hematological toxicity, both olaparib and AZD6738 should be held until resolution of toxicity to an Hg 9 Grade 2 for anemia only, or baseline. At the resolution of the first occurrence of any of these toxicities, no change should be made to the dose. At the second occurrence, upon resolution of toxicity, AZD6738 should be reduced by the first dose reduction as indicated below. If despite this change, there is a third occurrence, upon resolution of toxicity, AZD6738 should be further reduced by the second dose reduction as indicated below. Olaparib should not be dose-reduced.

Please note that for simultaneous toxicities (for example, neutropenia and thrombocytopenia), if AZD6738 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 the guidance below; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle. Once dose is reduced, escalation is not permitted.

See Section 6.5.5 **Error! Reference source not found.** and

for dose reduction guidance for AZD6738 and olaparib respectively.

Maximum tolerated dose will be defined in the presence of optimal supportive care for the toxicity in question.

Individual stopping criteria:

Hepatic

- ALT or AST or ALP* > 5 x ULN
- ALT or AST or ALP* > 3 x ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%) [ALT or AST > 3 x ULN] and [total bilirubin > 2 x ULN or INR+ > 1.5 or other evidence of impairment to the synthesis function of the liver] * In the presence of bone mets assess bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver)

  + Unless patient is receiving warfarin

  Please refer to Appendix A. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law.

Cardiovascular

- Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes.

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Symptomatic orthostatic fall in systolic blood pressure of more than 20 mmHg compared to resting supine systolic blood pressure.

- **Error! Reference source not found.** and
- Dose interruption and stopping criteria
- Event Action
  - Grade 3-4 toxicity (1st event): Interrupt AZD6738 (max. 21 days), resume at the next lowest dose level when resolved (Grade ≤ 2 or returns to baseline).
  - Grade 3-4 toxicity (subsequent events): Stop treatment
  - Grade < 3 toxicity (all events): Decision to interrupt AZD6738 (max. 21 days) is at the Investigator's discretion. Resume at same dose prior to interruption.

Surgery

- Interrupt AZD6738 (max. 21 days), resume at full dose. AZD6738 should be stopped 3 days prior to surgery and resumed approx. 10 days later. If the wound has not healed a further 7 days are permitted prior to restarting AZD6738.
- No stoppage is required for biopsy procedures.

Vomiting

- If vomiting occurs shortly after AZD6738 is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.

Missed dose

- Allowed to take the scheduled dose up to two hours after the scheduled dose time. If greater than two hours, the missed dose should not be taken, and patient should continue with next dose at allotted time.
- All dose modification and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the CRF.

6.5.6 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within four weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with Dr. Simpkins and the Medical Director.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the study administration log by the patient and verified by the provider at the office visit.

Study treatment should be stopped at least three days prior to elective major surgery at the discretion of the investigator. After surgery study treatment may be restarted when the wound has stabilized, this may require more than the four-week limitation otherwise set for being off

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treatment and is acceptable. No stoppage of study treatment is required for minor procedures such as a needle biopsy or endoscopy.

Study treatment should be discontinued for a minimum of three days before a patient undergoes radiation treatment. If a patient requires radiation, management of the case should be discussed with the PI of the study, Dr. Simpkins, to determine whether indication for radiation meets criteria for progression of disease. Study treatment should be restarted within four weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to treatment may include orthostatic hypotension, asthenia, fatigue, and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

6.6 Concomitant and post-study treatment(s)

The use of any natural/herbal products or other traditional remedies is not permitted. Use of vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF).

6.6.1 Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy, or other novel agent) is to be permitted while the patient is receiving study medication.

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30-day follow-up period.

6.6.2 Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken while on protocol.

If there is no suitable alternative concomitant medication other than a potent inhibitor of CYP3A, the investigator must interrupt the doses of AZD6738 for the duration of the potent CYP3A inhibitor and wait for the required wash-out period (five half-lives) before dosing AZD6738 again. After randomization if the use of any potent inducers or inhibitors of CYP3A4/5 are considered necessary for the patient's safety and welfare, the investigator must contact the PI of the study, Dr. Simpkins. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

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Strong or Moderate CYP3A inducers

Other strong (e.g. phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide, and St John's Wort) and moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil) of CYP3A should not be taken while on protocol.

If the use of any strong or moderate CYP3A inducers are considered necessary for the subject's safety and welfare this could diminish the clinical efficacy of the treatment.

If a subject requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy.

P-gp inhibitors

Co-administration of Pgp inhibitors or inducers may affect exposure to AZD6738 and, therefore, they should not be co-administered with AZD6738. If the use of any inhibitors or inducers of Pgp are considered necessary for the subject's safety and welfare, the investigator must interrupt AZD6738 for the duration of the Pgp inhibitor or inducer and wait for the required wash-out period of the Pgp modulator (five half-lives) before dosing ceralasertib again.

Effect of olaparib on other drugs

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K, BRCP.

AZD6738 is also a substrate of BCRP. Co-administration of strong BCRP inhibitors or inducers may affect exposure to AZD6738; therefore, it is recommended that the investigators must interrupt AZD6738 for the duration of the strong BCRP inhibitor or inducer and wait for the required wash-out period of the BRCP modulator (five half-lives) before dosing AZD6738 again.

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19, and P-gp.

The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib. Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Effect of AZD6738 on other drugs

AZD6738 is a potential inhibitor of CYP1A2, CYP2C8 and CYP2C9 as well as an inducer of CYP3A4 and CYP1A2. Caution should be applied with co-administration of drugs that are either completely metabolized by CYP1A2, CYP2C8, CYP2C9 and/or CYP3A4 or that are substrates of CYP1A2, CYP2C8, CYP2C9 and/or CYP3A4 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolized by CYP1A2, CYP2C8 and/or CYP2C9 may be increased and exposure of other drugs metabolized byCYP3A4 and/or CYP1A2 may be reduced. Refer to Appendix E for additional guidance.

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AZD6738 is an inhibitor of OATP1B1 and BCRP. Caution should be applied with co-administration of substrates of OATP1B1 and/or BCRP as ceralasertib may increase their exposure. Refer to Appendix E for additional guidance.

Anticoagulant Therapy

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

Anti-emetics/Anti-diarrheal

If a subject develops nausea, vomiting and/or diarrhea, then these symptoms should be reported as AEs and appropriate treatment of the event given.

Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at screening, provided the site investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a subject undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Administration of other anti-cancer agents

Subjects must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Subjects may continue the use of bisphosphonates or denosumab for bone disease.

6.7 Treatment compliance

A medication explanation sheet will be given to each subject. This explanation sheet will include how to take each study drug. It will include that there are extra tablets and those are not to be taken by the subject unless approved by their physician.

Pill boxes for AZD 6738 will be given to each patient. The pill box will be labeled with the days to take the AZD6738.

A fresh drug log will be given to the subject at each new cycle. The research coordinator will indicate which days the patient is to take AZD6738 on the study diary. The subject will be instructed to mark each dose of study drug she takes on the log. When the subject comes for each study visit she will bring the bottle and the log. The pills will be counted and correlated with the tabulations on the log. Reasons for noncompliance will be recorded and analyzed.

6.7.1 Accountability

The oncology pharmacist at each site will dispense the drug and receive the bottles on their return.

Unused study drug will be recorded and destroyed according to each hospital policy after the monitoring visit.

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6.8 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision
- If the investigator believes it is in the best interest of the subject to discontinue participation in the study
- Unexpected and possibly related adverse event/s grade 3 or higher at the discretion of the site PI
- Prolonged hematologic toxicity
- Any toxicity that prevents treatment for four consecutive weeks
- Severe noncompliance with the study protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Any new primary malignancy
- Progression of disease as defined by RECIST 1.1. CA125 alone is not sufficient to define progression
- In certain circumstances, treatment may be continued beyond RECIST 1.1 if the treating physician feels the patient is receiving clinical benefit after discussion and approval with the Overall study PI.

6.8.1 Procedures for discontinuation of a subject from investigational product (End of treatment)

If a subject discontinues treatment, evaluation will consist of:

- CT scan chest, abdomen, pelvis with oral and intravenous contrast
- H & P, including ECOG and weight
- Laboratory studies
- Cell free DNA
- Peripheral blood mononuclear cells
- Plasma
- Tumor Biopsy if safe/feasible

6.9 Withdrawal from study

If a subject is withdrawn from study she will only be replaced if she had received less than four weeks of therapy.

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7 COLLECTION OF STUDY VARIABLES

7.1 Recording of data

The data will be recorded in the study database housed at the University of Pennsylvania.

7.2 Data collection at enrollment and follow-up

Data collected at enrollment will include:

- Date of birth (or instead 'age' if local data privacy laws prevent the capture of birth date)
- Sex and race (and/or 'ethnicity' instead according to local laws)
- Weight and height
- Standard medical and surgical history
- Physical examination as appropriate including resting pulse and blood pressure measurement
- Results of enrollment laboratory studies
- CTCAE 5.0
- Pathology results from diagnosis and enrollment biopsy
- Imaging results as defined by RECIST 1.1

7.3 Enrollment procedures

If a patient would like to screen for the trial, informed consent will be obtained. This includes verbal discussion, an opportunity to review the written consent and once patient endorses their decision to participate, the informed consent form signed and dated.

A HIPAA compliant platform (ex: EPIC) may be used to conduct remote visits and the informed consent procedures. Only HIPAA compliant platforms are satisfactory for securing and protecting a patient's HIPAA privacy rights.

At this point enrollment data will be collected:

- H&P, including ECOG, weight, and blood pressure
- Baseline assessment of CTCAE 5.0 criteria
- EKG (Triplicate EKGs 2-5 minutes apart)
- CT scan chest, abdomen, pelvis with oral and intravenous contrast
- CA-125
- PT/PTT/INR
- Laboratory studies
- Research blood (cell free DNA, peripheral blood mononuclear cells, plasma)
- Tumor biopsy

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Each subject will be assigned a unique enrollment number.

- Subjects at the University of Pennsylvania will be assigned a 100 series numbers.
- Subjects at Johns Hopkins University patients will be assigned a 200 series number.
- Subjects at Harvard University will be assigned a 300 series number.

The Sponsor will review all patients deemed eligible for enrollment from other study sites (Johns Hopkins University or Harvard University) and agree that patient meets eligibility criteria prior to administration of study drug.

7.4 Study procedures

- Cycle 1, Day 1
  - CTCAE 5.0 assessment of adverse events
  - H & P, including ECOG, weight, and blood pressure
  - Laboratory studies
  - Assessment of CA-125
  - Dispensation of IP
- Cycle 1, Day 7
  - CTCAE 5.0 assessment of adverse events
  - H & P, including ECOG, weight, and blood pressure
  - Laboratory studies
  - DLT assessment (only for cohort D part I)
- Cycle 1, Day 15
  - CTCAE 5.0 assessment of adverse events
  - H & P, including ECOG, weight, and blood pressure
  - Laboratory studies
  - DLT assessment (only for cohort D part I)
- Cycle 2, Day 1
  - CTCAE 5.0 assessment of adverse events
  - H & P, including ECOG and weight, and blood pressure
  - Laboratory studies
  - DLT assessment (only for cohort D part I)
  - Assessment of CA-125
  - Dispensation of IP
  - Research blood draw

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- Cycle 2, Day 7 (or last day of olaparib/AZD6738 combination for Cycle 2) (Cohorts A-C)
  - Tumor biopsy
  - Research blood and PK lab draw
- Cycle 2, Day 14 (or last day of olaparib/AZD6738 combination for Cycle 2) (Cohort D)
  - Tumor biopsy
  - Research blood and PK lab draw
- Cycle X, Day 1
  - CTCAE 5.0 assessment of adverse events
  - H & P, including ECOG and weight
  - Laboratory studies
  - Assessment of CA-125
  - Dispensation of IP
  - Imaging as required by imaging schedule

7.5 Follow-up procedures

If off trial because the subject demonstrated a complete response, combination Olaparib and AZD6738 may be continued until progression. If the subject has a CR or PR and decides to stop treatment, the subject will be followed every 3-4 months per standard of care by a clinic visit (including an H&P, ECOG status, weight and blood pressure, CTCAE 5.0 safety evaluation), imaging, and a CA-125 which is standard of care. After completion of treatment, subjects will be contacted by phone or seen in the office every 3-4 months until progression or death.

Subjects who stop treatment because of toxicity will be followed at the discretion of the provider, until recovery to a new baseline or recovery to Grade 1 or to commencement of a new therapy. Subjects with ongoing AEs who have progression of disease and discontinue study drug, will be followed until AEs resolved to a new baseline or Grade 1 or commencement of a new therapy.

7.6 Efficacy

Response to treatment will be measured according to RECIST 1.1 criteria.

Complete response will be defined as the disappearance of all target lesions. All lymph nodes must be less than 10mm in short axis.

Partial response will be defined as a 30% decrease in the sum of the diameters of the target lesions. Stable disease will be defined as a change in sum of the diameters that does not meet criteria for progressive disease or partial response.

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Progressive disease will be defined as either:

- An increase in the sum of diameters of target lesions of at least 20%;
- The comparison will be made to the smallest sum while the patient was on study;
- The absolute increase must be at least 5mm or;
- The appearance of new target lesion(s).

7.7 Safety: Adverse Events and Serious Adverse Events

7.7.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

Events which are unequivocally due to disease progression should not be reported as AEs. This includes symptoms of metastasis or metastasis itself.

Abnormal Laboratory Values

A clinically significant laboratory abnormality should be documented as an adverse event if any of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management.

In case a subject shows an AST or ALT $\geq$ 3x ULN or total bilirubin $\geq$ 2x ULN, refer to Appendix A. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law for further instructions.

Dose Limiting Toxicity

Definition of DLT

A DLT is defined as any toxicity during the period of Cycle 1 (i.e., from dosing on Cycle 1, Day 1 until the last day of dosing in Cycle 1), which includes:

1. Hematological toxicities as follows:
    - Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting longer than 4 consecutive days

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- Grade 3 neutropenia (ANC ≥500 to <1000 cells/mm^3) of any duration accompanied by fever ≥ 38.5°C and/or systemic infection
- Grade 3 thrombocytopenia (25,000 to <50,000/mm^3) with bleeding
- Any other confirmed hematological toxicity ≥ CTCAE 5.0 Grade 4 (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e. a suspected spurious value)

2. Non-hematological toxicity ≥ CTCAE 5.0 Grade 3 including:
   - Laboratory abnormalities (a repeat may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e. a suspected spurious value)
   - QTc prolongation (> 500 msec)

3. Any other toxicity that is greater than that at baseline, and is clinically significant and/or unacceptable, and does not respond to supportive care.

4. Any event, including significant dose reductions or omissions, judged to be a DLT by the SRC.

A DLT excludes:
- Alopecia of any grade
- Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all subjects should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment)
- Any toxicity clearly unrelated to AZD6738/olaparib combination e.g. solely related to the disease or disease-related process under investigation.

7.7.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is any AE that, in the view of either the investigator or the Sponsor, is:
- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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7.7.3 Classification of an Adverse Event

Severity of Event

All AEs will be assessed using CTCAE 5.0.

For adverse events (AEs) not included in CTCAE 5.0, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to Olaparib and AZD6738 assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. Relationship to each of the products (Olaparib and AZD6738) must be assessed.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to Olaparib and/or AZD6738 administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the Olaparib and/or AZD6738 (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the Olaparib and/or AZD6738, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial study drug). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

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- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to Olaparib and/or AZD6738 administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the Olaparib and/or AZD6738) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Unrelated – The AE is completely independent of Olaparib and/or AZD6738 administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the Olaparib and/or AZD6738.

7.7.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects using the CTCAE 5.0 at each study visit. Participants will be monitored by medical histories, physical examinations, and laboratory testing. If CTCAE 5.0 grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE 5.0 Grade 1-5)
2. Duration (start and end dates)
3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].

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5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

7.7.5 Events of Special Interest

Olaparib

Adverse Events of Special Interest (AESI) are MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

AZD6738

There are no AESI with AZD6738.

Combination olaparib and AZD6738

There are no AESI with combination olaparib and AZD6738.

7.7.6 Adverse Event Reporting

Reporting Period

Adverse events will be recorded using the terminology and severity grade established by CTCAE 5.0.Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the *30-day follow-up* period. If withdrawn 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 or Grade 1 or new baseline.*

All new AEs occurring during that period must be recorded. All study-related toxicities/SAEs must be followed until resolution or Grade 1 or new baseline, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

Investigator Reporting: Notifying the Study Sponsor
SAEs
Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the Sponsor within 24 hours of learning of its occurrence.

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Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the SAE report to the University of Pennsylvania Project Manager.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE. The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

AESI

AESIs must be reported to the Sponsor within 24 hours of learning of its occurrence.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB of record and other local regulatory groups per the local requirements.

7.7.7 Serious Adverse Event Reporting

Investigator to Sponsor

The study clinician will immediately report to the Sponsor any serious adverse event, whether or not considered related to Olaparib and/or AZD6738, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the Olaparib and/or AZD6738 caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the Olaparib and/or AZD6738 and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the Sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form).

The SAE reports to the Sponsor should be sent to the University of Pennsylvania Project Manager.

Sponsor to FDA
The study Sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction per applicable regulations. In addition, the Sponsor must notify FDA and all participating investigators of potential serious risks, from clinical trials or any other source, as per the applicable regulations.

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Sponsor to Funding Sponsor (Astra Zeneca)
When the Sponsor informs the FDA of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, the Sponsor will concurrently forward all such reports to the drug manufacturer. It is the responsibility of the Sponsor to ensure reports are submitted to the drug manufacturer per the agreement (i.e. at the same time as they are submitted to the FDA).

*A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- External Scientific Research (ESR)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and the drug manufacturer ESR reference number

*Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study drugs*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.
If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the drug manufacturer.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to the drug manufacturer 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 the Sponsor and drug manufacturer, whether or not considered causally related to the investigational product.

Disease progression
Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

New cancers
The development of a new primary cancer (including skin cancer) should be regarded as an AE. New primary malignancies 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.

Lack of efficacy
When there is deterioration in the condition for which the study treatment(s) is being used there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition the deterioration should be considered to be a lack of efficacy and not an AE.

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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 as an SAE within 24 hours (see Section 7.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

7.7.8 Laboratory safety assessment

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and absolute neutrophil count or segmented neutrophil count and band forms should be performed at Cycle 1, Day 1, Cycle 1, Day 7, Cycle 1, Day 15 and then prior to each subsequent cycle. 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 as clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, and albumin) should be performed at Cycle 1, Day 1, Cycle 1, Day 7, Cycle 1, Day 15 and then prior to each subsequent cycle.

These tests will be performed by the hospital's laboratory, Lab Corps, or Quest. Additional analyses may be performed if clinically indicated.

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

In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix A. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law, for further instructions.

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7.8 Physical examination

At enrollment and then prior to each cycle patients will undergo a thorough physical exam. ECOG performance status will be recorded at each visit.

7.8.1 EKG

12 lead triplicate EKGs 2-5 minutes apart will be performed as part of screening and as clinically indicated. Each EKG will be read by institutional cardiology team per hospital protocol.

Twelve-lead EKGs will be obtained after the subject has been rested in a supine position for at least 2-5 minutes in each case. ECGs will be recorded at 25 mm/sec. Required measurements include heart rate, P and QRS durations, PR, QT and QT intervals. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original EKG traces must be stored in the patient medical record as source data.

7.8.2 Vital signs

Vitals signs (body temperature (°C), blood pressure, pulse, respiratory rate, oxygen saturation) will be measured and recorded at enrollment and then prior to each new cycle of treatment.

If the patient is exhibiting signs of orthostasis, blood pressure and pulse will be taken as though assessing for orthostasis. After a 10-minute period of reset, blood pressure and pulse will be measured supine, sitting, and standing. All values will be recorded.

7.8.3 Bone marrow or blood cytogenetic analysis

Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for patients with prolonged hematological toxicities. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to the drug manufacturer. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical record.

7.8.4 Volume of blood

The total volume of blood that will be drawn from each subject in first two cycles of this study is as follows:

Table 15. Volume of blood to be drawn from each subject

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Haematology	5	8	40
Chemistry	5	8	40
Coagulation	5	1	5

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Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Blood for research	50	3	150
Blood for pk studies	10	3	30
Total			265

7.9 Handling, storage and destruction of biological samples

The samples will be stored for a maximum of 15 years from the date of a subject's last visit. Each patient will be assigned a unique identifier at enrollment and all data generated by samples from that patient will be similarly labeled with the same primary identifier. The database linking the identifiers with the patients will be held by the study sponsor and held securely to maintain confidentiality.

Given each patient will have multiple samples over multiple time points, the unique identifier will be placed on each sample with a numeric modifier. There will be samples collected at three potential time points: A, B, and C. Specimens taken at each time point will be labeled: A1 for the first sample, A2 for the second, A3 for the third, A4 for the fourth, and A5 for the fifth sample.

Where genetic analysis will be undertaken the processes adopted for coding and storage of samples will be more stringent in order to maintain patient confidentiality. The study staff working in the laboratories will not have access to any identifying information, only the unique identifiers.

Once all data has been generated from the samples and clinical data needed collected, the datasets will be merged, each patient will be given a second unique identifier. All identifying information except the second unique identifier will be removed from the database. The code linking the first and second unique identifiers will be held by the study PI. This PHI-free database will be used for statistical analysis and publication preparation.

7.9.1 Labeling and shipment of biohazard samples

The same labeling system will be used at all sites. When samples must be shipped, the unique identifier labels will be applied prior to shipment.

No infectious samples will be shipped. All archival tumor samples should be shipped at ambient temperature.

7.9.2 Chain of custody of biological samples

A full chain of custody is maintained for all samples at all times. When samples must be shipped from one study location to another, two persons will validate the samples and labels prior to shipment. The package will be opened by two persons and the specific samples received verified and this will be documented.

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7.10 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, if samples have not been used, they will be disposed of/destroyed, and the action documented.

The Principal Investigator:

- Ensures that biological samples (if remaining) from that subject are immediately identified, destroyed, and the action documented;
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site;
- Ensures that the subject is informed of the confirmed sample(s) disposal.

If the subject withdraws consent from the blood exploratory objective assays, the subject will be withdrawn from the study. If the subject declines biopsy either at enrollment or following Cycle 1 the subject will be withdrawn from study. Performance of a biopsy when the patient comes off study is optional, although preferred and encouraged. In the event the tumor has responded to an extent that biopsy after Cycle 1 is not feasible or safe, the subject will be allowed to continue on study. Safety and feasibility of biopsy at enrollment is an inclusion criterion.

8 ETHICAL AND REGULATORY REQUIREMENTS

8.1 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, and applicable regulatory requirements.

8.2 Subject data protection

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject.

8.3 Ethics and regulatory review

All protocols and documents will be reviewed by the Penn (central) IRB and acknowledged by local IRBs as required. All staff will demonstrate training in the ethical conduct of research.

8.4 Exceptions and Deviations

Exceptions and deviations will be submitted to the Penn IRB and other Penn entities (such as CTSRMC) for approval/acknowledgement, according institutional guidelines.

8.5 Informed consent

Each patient will complete the informed consent process. Enrollment and study drug administration will not commence until the informed consent process is complete and documented with original signatures and dates.

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8.6 Changes to the protocol and informed consent form

Changes to the protocol and informed consent form will be minimized. When necessary the new protocols will not take effect until approval from the Penn (central) IRB and acknowledgement from local IRBs are obtained as required.

If the changes are of a critical nature as determined by the PI, enrollment will be placed on hold pending IRB approval of the changes. If the changes are of an administrative or non-critical nature study enrollment will continue while the IRB approval is obtained.

8.7 Audits and inspections

Audits and inspections of each site will occur prior to study initiation, after enrollment of half the intended patients, and at the conclusion.

9 STUDY MANAGEMENT

9.1 Training of study site personnel

Prior to each study site initiating enrollment, the Sponsor will ensure the site is trained on the protocol and all operating procedures. The protocol will be augmented with a practical operating procedures manual that each site will be given. This will include all critical documents (e.g. protocol, consent, list of prohibited medications, patient timetable, and drug log) and explanation of each step for the study process.

9.2 Monitoring of the study

9.2.1 Source data

All study data will be collected at individual sites and then entered into the study database created by and housed at the University of Pennsylvania.

9.3 Study timetable and end of study

After subject's enrollment on study, all data will be collected and entered into the database within approximately two weeks +/- 7 days. Patients who are experiencing a complete response, partial response, or stable disease will be permitted to continue treatment until progression of disease or adverse effect leads to delay of treatment for more than four consecutive weeks.

10 DATA MANAGEMENT

Data will be held at the University of Pennsylvania in the study database.

11 EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

RECIST 1.1 will be used to evaluate for compete response, partial response, stable disease, and progression of disease.

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Progression free interval will be defined as date of study enrollment (assignment of unique identifier) to date of progression. The date of progression will be determined by physical exam findings of disease progression or RECIST 1.1 criteria for imaging.

11.2 Calculation or derivation of safety variable(s)

Safety parameters will be assessed as a percentage of patients who experience each CTCAE 5.0 at each grade.

12 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

1. Primary analysis set: Efficacy will be analyzed on all patients who initiate treatment regardless of number of doses of treatment they receive and have at least one response evaluation available. Patients who are withdrawn prior to initiating treatment will not be included in the analysis.
2. Exploratory analyses sets:
    a. Only those patients who complete two or more cycles of treatment;
    b. Only those patients who have received prior PARP inhibitor.

12.1.2 Safety analysis set

Safety will be analyzed on all patients who initiate treatment regardless of number of doses of treatment they receive.

12.2 Methods of statistical analyses

The primary objectives for Cohorts A to C of this trial are to determine the safety and objective response rates (ORRs) to the combination of olaparib and AZD6738 in subjects with recurrent ovarian cancer. Given the different olaparib single agent activity in platinum-sensitive versus resistant recurrent ovarian cancer (Liu J et al, Lancet Oncology, 2011; Gelmon K et al, Lancet Oncology, 2011; Audeh MW, Lancet, 2010; Fong, NEJM, 2009), this study will examine two cohorts separately: recurrent platinum-sensitive cohort (Cohort A) and platinum-resistant cohort (Cohort B). The third cohort (Cohort C) of PARP inhibitor (PARPi) resistant subjects (i.e., subjects who have progressed on PARPi monotherapy) will also be analyzed separately. Cohort D includes a dose and schedule finding phase (Part I) and an expansion phase (Part II) which will also be analyzed separately. The objectives for Cohort D of the trial is to determine maximum tolerated dose (MTD) and an alternative dose and schedule of the combination in Cohort D, using a higher dose of AZD6738 and a lower dose of olaparib than that tested in Cohorts A to C. All analysis will be completed according to intent to treat principle. Statistical analyses will not be done on the combined cohorts. This trial will be open at the University of Pennsylvania, Johns Hopkins University, and Harvard University.

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Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), serious AEs (SAEs), laboratory tests, and vital signs. Frequency and severity (based on CTCAE 5.0 grades) of AEs will be summarized by system organ class, preferred term, and relations to study drug. The frequency of Grade 3 and 4 AEs will be summarized separately. Protocol-defined DLT for Cohort D Part I portion of the trial will be described descriptively and exact 95% confidence interval for the DLT rate or AE rates will be computed using binomial distribution. Additionally, tolerability will be examined by computing the percentage of subjects experienced dose modification and/or discontinue treatment due to an adverse event. Changes or abnormal laboratory values and vital signs from time of treatment initiation will be summarized descriptively.

Objective response rate (ORR) is defined as the proportion of patients achieving CR or PR for the platinum-resistant cohort for the platinum-sensitive cohort as assessed by the investigator per RECIST 1.1. Point estimate and 90% exact confidence interval (CI) will be computed.

Progression-free survival (PFS) is defined as the time from enrollment to the time of disease regression, or death by any causes (in the absence of disease progression). Disease progression will be determined by investigator per RECIST criteria. Patients without documented disease progression will be censored at last tumor evaluation. Kaplan-meier curves and median survival time and 95% CI will be computed. Change values from pre-treatment values in immune markers, cell-free DNA, and other correlative endpoints will be associated with the treatment response using independent-sample t-test or Wilcoxon rank sum test. The predictive value of the newly developed PET–labeled PARPi probe, 18F-fluorthanatrace (FTT) on treatment response will be explored using ROC curve analysis. Any secondary evaluations or exploratory analyses performed will be done in an exploratory fashion using descriptive statistics, with results presented without any formal adjustment for multiple comparisons. All tests if performed will be two-sided.

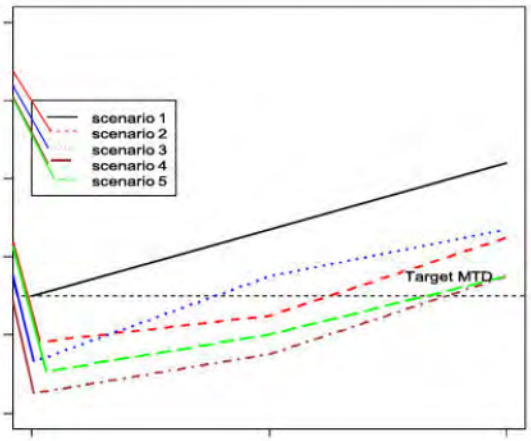


Figure 16. Graph of dose limiting toxicity curves

12.2.1 Interim analyses

For Cohorts A and B, Simon two-stage design will be implemented in this trial for the recurrent platinum-sensitive cohort and platinum-resistant cohort separately. At the end of the first stage, treatment cohort with objective response rate lower than the pre-determined rate will be terminated. A review of the safety and tolerability of the combination will take place alongside efficacy at the interim. Dose modification is permitted.

12.3 Determination of sample size

This trial will consist of four cohorts. Sample size planned for the first two cohorts (Cohort A: platinum-sensitive, Cohort B: platinum-resistant) is based on the objective to determine if the combination would rule out a 20% ORR (null hypothesis) and

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result in an ORR consistent with 40% (alternative hypothesis) in patients with recurrent platinum-sensitive ovarian cancer, mostly with BRCA wild-type. In addition, we would rule out a 5% ORR (null hypothesis) and result in an ORR consistent with 20% (alternative hypothesis) in patients with recurrent platinum-resistant ovarian cancer. The choices of null and alternative hypotheses were based on existing literature (Liu J et al, Lancet Oncology, 2011; Gelmon K et al, Lancet Oncology, 2011; Audeh MW, Lancet, 2010; Fong, NEJM, 2009). Using a Simon optimal two-stage phase II design with alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), the first stage will treat 17 platinum-sensitive and 12 platinum-resistant patients. If 4 out of the 17 or 1 out of the 12 patients responded then the trial will continue to the second stage for a total of 37 and 37 patients treated, respectively. If total number of responding is less than or equal to 10 (platinum-sensitive) or 3 (platinum-resistant) out of the 37 patients in the cohort then the combination will be rejected. Under the null hypotheses, the probability of early termination is 55% for platinum-sensitive cohort and 54% for platinum-resistant cohort. Due to exploratory nature of Cohort C, the platinum-sensitive, acquired PARPi resistant cohort (Cohort C), formal sample size justification is not performed. Approximately 12 patients will be treated in this cohort. If 3 responses (PR or CR) are found (i.e., probability of response at least 10% based on 90% one-sided confidence interval), the protocol will then be amended for include an expansion phase for this cohort.

The dose finding portion of Cohort D will implement the BOIN design to find MTD. The BOIN design can be implemented in a similar way as the traditional 3+3 but has been shown to have superior operating characteristics that are comparable to model-based designs such as continual reassessment method (CRM). The target DLT rate for the MTD is set at 30% and two alternatives; the highest DLT rate that is deemed as sub-therapeutic is 25% and the lowest DLT rate that is deemed as overly toxic is 35%. The 25% and 35% DLT rates were selected based on the prior Phase I experience with AZD6738. Furthermore, to avoid assigning too many patients to the overly toxic doses, a dose level will be eliminated when the posterior probability is greater than 95% that the toxicity rate of a dose level is >30% if at least 3 patients are treated at the dose level. Dose escalation will continue to enroll and treat patients in a until a maximum of 12 patients are treated and evaluable for DLT or the maximum 30 patients planned for this Phase is reached. The starting dose level will be dose level 1. Dose escalation or de-escalation for the first three subjects will be done based on one subject at a time treated sequentially with 28 days DLT period between each subject. If a DLT is observed in the first subject under dose level 1, we will continue to treat at dose level 1 until either dose level 1 is eliminated for overly toxic or we are able to escalate to the next dose level. The remaining dose escalation or de-escalation will be done in a cohort of three subjects without staggering between subjects.

The dose escalation or de-escalation rules to evaluate the 3 proposed dose levels are provided in **Error! Reference source not found.**and **Error! Reference source not found.**. After the dose (de)escalation is completed, the MTD will be selected based on isotonic regression as specified in Liu and Yuan. Based on 5000 simulations that explored five true monotonic toxicity curves covered a wide range of scenarios (Figure 16), the operating characteristics of the proposed design indicated we will be able to select the true MTD with high probabilities (between 44% to 69% for scenarios 1 to 5) and allocates more patients to the dose levels with the DLT rate closet to the target of 30%. The total number of patients to be enrolled during the dose escalation part (Part I) will

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vary depending on the underling-dose-toxicity relationships and the number of doses tested before determining MTD. At most 30 patients will be allocated to Cohort D Part I. If not all three (3) dose levels explored are tolerable or if the MTD is lower than the highest dose level 3, we will discuss with Safety Review Committee (SRC) to explore other alternative dosing schedules (e.g., level 4, and level 5 on

) using the remaining patients from the original 30 maximum number of patients allocated to Cohort D Part I. For Cohort D Part II, we will treat an additional 12 patients at the dosing schedule determined from Part I and after the evaluation by SRC. The overall sample size across all four cohorts will be 128 patients.

It is expected that 4-6 patients per month may enroll onto this trial at the University of Pennsylvania, Johns Hopkins University, and Harvard University. Thus, it is expected that two years may be required in order to enroll up to 128 evaluable (as define by efficacy analysis set) patients. In order to allow for a number of in-evaluable patients, the accrual ceiling will be set at 140 patients. Patients are evaluable if they initiate treatment with combined therapy.

12.4 Data monitoring committee

The data safety monitoring committee will review the safety data at the end of stage 1, when efficacy is also assessed, prior to expanding the platinum-sensitive (Cohort A) and platinum-resistant (Cohort B) cohorts to the maximum of 37 patients each and throughout the trial for Cohorts C and D. The safety data will be reviewed alongside the efficacy response data in the interim analysis to ensure the risk benefit ratio supports expansion. Additionally, side effect profile will be followed closely with each cycle of chemotherapy. Management of toxicities will be based on the management strategies employed with olaparib.

12.5 Overdose

There is currently no specific treatment in the event of overdose with olaparib or AZD6738 and possible symptoms of overdose are not established.

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 Sponsor informs 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 Sponsor 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.

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14 Appendix A. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.5.5.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the study drug.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study drug irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the study drug, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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When a subject meets any of the identification criteria, in isolation or in combination, the study staff will immediately send an alert to the treating physician and the Principal Investigator.

- The Principal Investigator will without delay review each new laboratory report and determine whether the subject meets PHL criteria (see "Identification of Potential Hy's Law Cases" for definition) by reviewing laboratory reports from all previous visits including unscheduled visits and labs completed at a local laboratory.

If the identification criteria are met from central or local laboratory results, then without delay:

- Johns Hopkins University and Harvard University: Notify University of Pennsylvania and follow steps outlined in "Potential Hy's Law Criteria met" section below.
- University of Pennsylvania: Notify AstraZeneca and follow steps outlined in "Potential Hy's Law Criteria met" section below.

Follow-up

Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria, the Investigator will:

- Johns Hopkins University and Harvard University: Notify University of Pennsylvania that subject does not meet PHL criteria and follow steps outlined in "Potential Hy's Law Criteria met" section above.
- University of Pennsylvania: Notify AstraZeneca that subject does not meet PHL criteria and follow steps outlined in "Potential Hy's Law Criteria met" section above.

Potential Hy's Law Criteria met

If the subject meets PHL criteria, the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting study treatment (See "Actions Required When Potential Hy's Law Criteria Are Met Before and After Starting Study Treatment")

- Johns Hopkins University and Harvard University: Notify University of Pennsylvania.
- University of Pennsylvania: Notify AstraZeneca.

The study staff / treating physician will contact the Principal Investigator to discuss and agree on an approach for the subject's follow-up and the continuous review of data. Subsequent to this contact, the study staff / treating physician will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Principal Investigator.
- Document as appropriate in the subject's chart, study records, and database.
- Follow-up with the Principal Investigator on new findings.

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- If at any time (in consultation with the Principal Investigator) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than three weeks after the biochemistry abnormality was initially detected, the Principal Investigator contacts the study stuff / treating physician in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury (DILI) caused by the study drug. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to processes described above.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over three weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assess to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

Actions Required When Potential Hy's Law Criteria Are Met Before and After Starting Study Treatment

This section is applicable to subjects with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

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At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the subject's condition* compared with the last visit where PHL criteria were met.
- If there is no significant change no action is required.
- If there is a significant change:
    - Johns Hopkins University and Harvard University: Notify University of Pennsylvania.
    - University of Pennsylvania: Notify AstraZeneca.

*A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Principal Investigator in collaboration with study staff / treating physician should determine the cause for the previous occurrence of PHL criteria being met and answer the following questions:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection, or liver disease?
- Did the subject meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in "Actions Required When Potential Hy's Law Criteria Are Met Before and After Starting Study Treatment"?

If No to both: follow the process described in "Potential Hy's Law Criteria met"

If Yes to either: Determine if there has been a significant change in the subject's condition* compared with when PHL criteria were previously met.

- If there is no significant change no action is required.

*A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Principal Investigator; this may be in consultation with the study staff / treating physician if there is any uncertainty.

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References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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15 Appendix B. Subject Dosing Diary

Subject Dosing Diary Cohort A, B, C
Olaparib

Subject: _____

Date: _____

Study Day/Visit: Cycle: _____ Day: _____

Bring this form and all used and unused study drug in the original packaging every time you come for a visit to the clinic.

Instructions:

Please take Olaparib _____ mg twice daily on days 1-28.

If possible, you should take the morning and evening dose at the same time every day.

Record the dose taken in the morning and evening, record the date and times you take your medication, below. If you are more than 2 hours late in taking either dose, skip that dose.

There are extra tablets in each bottle. Do not take them unless approved by your physician.

Bring any unused tablets in their original bottles and your completed dosing card to each appointment.

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Date	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Subject Dosing Diary
AZD6738- Cohorts A, B, C

Subject: _____

Date: _____

Study Day/Visit: Cycle: _____ Day: _____

Bring this form and all used and unused study drug in the original packaging every time you come for a visit to the clinic.

Instructions:

Please take AZD 6738 _____mg in morning on days 1-7. This will be on the following dates: _____ for this cycle.

If possible, you should take the morning dose at the same time every day.

Record the date and times you take your medication below.

If you are more than 2 hours late in taking either dose, skip that dose.

There are extra tablets in each bottle. Do not take them unless approved by your physician.

Bring any unused tablets in their original bottles and your completed dosing card to each appointment.

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Date	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Subject Dosing Diary
Olaparib- Cohort D

Subject: _____

Date: _____

Study Day/Visit: Cycle: _____ Day: _____

Bring this form and all used and unused study drug in the original packaging every time you come for a visit to the clinic.

Instructions:

Please take Olaparib _____ mg twice daily on days 1-28.

If possible, you should take the morning and evening dose at the same time every day.

Record the dose taken in the morning and evening, record the date and times you take your medication, below. If you are more than 2 hours late in taking either dose, skip that dose.

There are extra tablets in each bottle. Do not take them unless approved by your physician.

Bring any unused tablets in their original bottles and your completed dosing card to each appointment.

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Date	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)	___/___/___ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Subject Dosing Diary
AZD6738 - Cohort D

Subject: _____

Date: _____

Study Day/Visit: Cycle: _____ Day: _____

Bring this form and all used and unused study drug in the original packaging every time you come for a visit to the clinic.

Instructions:

Please take AZD 6738 _____mg in the morning and _____ mg in the evening on days _____.
This will be on the following dates: _____ for this cycle

If possible, you should take the morning and evening dose (if any) at the same time every day.

Record the date and times you take your medication below.

If you are more than 2 hours late in taking either dose, skip that dose.

There are extra tablets in each bottle. Do not take them unless approved by your physician.

Bring any unused tablets in their original bottles and your completed dosing card to each appointment.

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Date	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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Date	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)	___/____/____ (dd/mm/yr)
	Morning dose	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**	**Morning dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							
	Evening dose	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**	**Evening dose**
Time of dose (hr:min)							
Total # of tablets taken							
Was food taken with dose?							

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16 Appendix C. Medication Instructions - Cohorts A, B, C

Patient Medication Instructions

Suggested Dosing:

For ease of administration, it is suggested that you take your pills the following way:

On Days 1-7 (AZD6738 and olaparib in the morning, olaparib only in the evening)

- In the morning, fast for at least two hours before taking any medication. Water is allowed during fasting period.
- Please take both medications (AZD6738 and olaparib) at the same time in the morning, with one glass of water. You can take the medication with sips of water on your biopsy date(s), if applicable.
- After taking the medications, please fast for at least one hour. Water is allowed during fasting period.
- 12 hours from the morning dose, please take your second olaparib dose. This can be taken with or without food.

On Days 8-28 (olaparib only, both morning and evening)

- Please take the first dose of olaparib in the morning.
- 12 hours from the morning dose, please take your second olaparib dose.
- Both doses can be taken with or without water and/or food.

If you find you are having GI upset when taking olaparib on an empty stomach, please talk to your doctor to ask about an alternative dosing schedule.

If you take the medications in any other way other than what is listed above, please clearly note this on you pill diary.

Important Notes BOTH Medications:

- Olaparib and AZD6738 may be stored at room temperature.
- Olaparib and AZD6738 should be swallowed whole and not chewed, crushed, dissolved, or divided.
- You will be provided extra pills for each study drug. Please do not take additional dose after the scheduled study days. (Days 1-7 for AZD6738, Days 1-28 for Olaparib)

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- If you vomit shortly after swallowing the tablets (either AZD6738 or Olaparib), the dose should be replaced *ONLY* if you can see and count all intact tablets AND you have spoken with a provider.

- If you should miss a scheduled dose for any reason, you are allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time (following specific directions for each drug as descripted below). If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken. Take the next dose as scheduled.

Important Notes AZD6738:

- AZD6738 will be taken orally (by mouth) ONCE daily on days 1 to 7 (dose: 160 mg). **AZD6738 pills are not to be taken on day 8 or after.**

- You must fast for at least 2 hours prior to taking AZD6738.

- You must take AZD6738 with a glass of water.

- You must fast for at least 1 hour after taking AZD6738.

- Avoid grapefruit juice, Seville oranges (including marmalade, juice, etc.), herbal supplements, and excessive sun exposure while taking AZD6738.

Important Notes Olaparib:

- Olaparib will be taken orally (by mouth) TWICE daily (dose: 300 mg).

- Tablets should be taken at the same time each day approximately 12 hours apart.

- On days 1-7, the morning dose should be taken on an empty stomach as above, with a glass of water. The evening dose can be taken with or without water and/or food.

- On days 8-28, both doses can be taken with or without water and/or food.

Other Notes:

- You should avoid certain foods, juices, and over the counter medications as they will potentially affect the absorption of your study drugs. Please avoid grape-fruit juice, Seville oranges (including marmalade, juice, etc.), herbal supplements, and other anti-cancer therapy. It is also recommended to avoid excessive sun exposure for the duration of the study.

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17 Appendix D. Medication Instructions - Cohort D

Patient Medication Instructions

Suggested Dosing: (Dates manually entered by coordinator)

For ease of administration, it is suggested that you take your pills the following way:

On Days _____ (AZD6738 and olaparib both morning and evening)

- Please take both medications (AZD6738 and olaparib) at the same time in the morning, with one glass of water. You can take the medication with sips of water on your biopsy date(s), if applicable.
- 12 hours from the morning dose, please take your second dose of both medications at the same time with one glass of water.
- For both morning and evening doses, please fast for at least two hours before taking any medication and for at least one hour after taking any medication.

On Days _____ (olaparib only, both morning and evening)

- Please take the first dose of olaparib in the morning.
- 12 hours from the morning dose, please take your second olaparib dose.
- Both doses can be taken with or without water and/or food.

If you find you are having GI upset when taking olaparib on an empty stomach, please talk to your doctor to ask about an alternative dosing schedule.

If you take the medications in any other way other than what is listed above, please clearly note this on you pill diary.

Important Notes BOTH Medications:

- Olaparib and AZD6738 may be stored at room temperature.
- Olaparib and AZD6738 should be swallowed whole and not chewed, crushed, dissolved, or divided.
- You will be provided extra pills for each study drug. Please do not take additional dose after the scheduled study days.
- If you vomit shortly after swallowing the tablets (either AZD6738 or Olaparib), the dose should be replaced *ONLY* if you can see and count all intact tablets AND you have spoken with a provider.

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- If you should miss a scheduled dose for any reason, you are allowed to take the scheduled dose up to a maximum of 2 hours after the scheduled dose time (following specific directions for each drug as descripted below). If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken. Take the next dose as scheduled.

Important Notes AZD6738: (Dose manually entered by coordinator)

Please take AZD6738 _____mg in the morning and _____ mg in the evening on days _____. This will be on the following dates: _____
AZD6738 pills are not to be taken outside these days of each cycle.

- You must fast for at least 2 hours prior to taking AZD6738.
- You must take AZD6738 with a glass of water.
- You must fast for at least 1 hour after taking AZD6738.

Avoid grapefruit juice, Seville oranges (including marmalade, juice, etc.), herbal supplements, and excessive sun exposure while taking AZD6738.

Important Notes Olaparib: (Dose manually entered by coordinator)

- Olaparib will be taken orally (by mouth) TWICE daily (dose: ____ mg) on days 1-28.
- Tablets should be taken at the same time each day approximately 12 hours apart.
- Doses taken in combination with AZD6738 as above, both morning and evening, should be taken on an empty stomach as above, with a glass of water.
- Doses on dates without AZD6738 can be taken with or without water and/or food.

Other Notes:

- You should avoid certain foods, juices, and over the counter medications as they will potentially affect the absorption of your study drugs. Please avoid grape-fruit juice, Seville oranges (including marmalade, juice, etc.), herbal supplements, and other anti-cancer therapy It is also recommended to avoid excessive sun exposure for the duration of the study.

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18 Appendix E. CYP3A Inhibitors and Inducers

Potent CYP3A Inhibitors	Potent CYP3A Inducers
boceprevir	apalutamide
ceritinib	avasimibe
clarithromycin	carbamazepine
cobicistat (GS-9350)	enzalutamide
conivaptan	ivosidenib
danoprevir / RIT	lumacaftor
elvitegravir / RIT	mitotane
grapefruit juice[a]	phenobarbital
idelalisib	phenytoin
indinavir	rifampin
indinavir /RIT	rifapentine
itraconazole	St John's Wort extract
ketoconazole	
LCL161	
lopinavir / RIT	
mibefradil	
mifepristone	
nefazodone	
nelfinavir	
posaconazole	
ribociclib	
ritonavir	
saquinavir	
saquinavir / RIT	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
VIEKIRA PAK2[b]	
voriconazole	

List created using the University of Washington Drug-Drug Interaction Database Jan 2012.
RIT=Ritonivir. Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity

[a] Double-strength grapefruit juice. Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g., 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<Update/delete this default footnote as required.

[b] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days

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19 Appendix F. Safety Review Committee

Safety Review Committee

Drug	AZD6738 and olaparib
Study Code	CAPRI

AZD6738 Safety Review Committee Remit

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19.1 Safety Review Committee Members Details

Role	Name	Core or invited member	Delegate name and email
Principal investigator University of Pennsylvania	[redacted]	Core	[redacted]
Principal investigator Johns Hopkins University	[redacted]	Core	
Principal investigator Brigham Hospital – Harvard University	[redacted]	Core	
Medical Director	[redacted]	Core	[redacted]
Research Coordinator University of Pennsylvania	[redacted]	Core	
Project Manager University of Pennsylvania	[redacted]	Core	
AstraZeneca Project Manager	[redacted]	Invited	
Phase I Trial Expert	[redacted]	Core	

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19.2 Draft Agenda for Safety Review Meetings

Agenda for Safety Review Meeting Cohort D CAPRI

ASTRAZENECA: AZD6738
SAFETY REVIEW COMMITTEE TELECONFERENCE AGENDA
MMM DD, YYYY
HH:MM XM EST

Telephone Number:
TBD

Attendees: (c) = core, (I) =Invited following each name, (D xxx) = delegate for *name of core member*

Agenda:
Example

• Clinical review of cohort X patients	Investigators
• Safety Data Review	AZ Medical Monitor
• ECG review	AZ Medical Monitor
• PK Data Review	Clinical Pharmacology Scientist
• Proposed escalation/de-escalation	All (If applicable)
• Recruitment plan for cohort /Study Module Part	Investigators
• A.O.B	

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19.3 Safety Review Committee Minutes Template

D5330C00004 (AZD6738)
SAFETY REVIEW COMMITTEE TELECONFERENCE MINUTES
MMM DD, YYYY
HH:MM XM EST

Attendees: (c) = core, (I) =Invited following each name, (D xxx) = delegate for *name of core member*
Meeting Minutes:

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19.4 CAPRI Cohort D Safety Review Committee Meeting Dosing discussion and Approval

The Safety Review Committee agreed on the following dose decision (please tick as appropriate):

Study Module _____

1. Increase the AZD6738 dose to _____mg ☐
2. Decrease the AZD6738 dose to _____mg ☐
3. Change AZD6738 dosing schedule to ☐
4. Increase the combination agent(s) dose to _____ ☐
5. Decrease the combination agent(s) dose to _____ ☐
6. Change dosing combination agent(s) schedule to ☐
7. Stop dosing ☐
8. Expand the cohort ☐
9. Other (please specify) _____ ☐

Next cohort dosing data:

Study Number	D5330C00004
Cohort number	
Dose: **Schedule:**	
Formulation strength XX mg **XX tablets XX daily**	

Comments and supporting information:

Signed: _____ Date: _____

PI or Medical Director

_____

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19.5 Additional data requirements for AZD6738 SRC/medical review

1. **Patient Summary Report**

Example template: PLACEHOLDER

2. **Lab data review**

    a. Lab data by dose cohort with flag for concerning data (trends)

        i. Whole lab data listings, with out of range data flagged

        ii. Listings both cumulative showing full data, and showing only new data since previous listing provided

        iii. Specific issues to be highlighted by the medical monitor

    b. Where there is an ongoing concern that is being actively monitored, plot lab value (or group of values) vs time for the individual patient, and for the cohort

    c. Where there is an ongoing concern that is being actively monitored, plot lab value (or group of values) vs AUC or Cmax for the cohort

    d. The following should be plotted per patient

        i. Neutrophil absolute counts vs time
        ii. ALT absolute value vs time
        iii. AST absolute value vs time
        iv. AlkPhos absolute value vs time
        v. Bilirubin absolute value vs time
        vi. Gamma GT absolute value vs time
        vii. Blood pressure absolute value vs time (at Cmax)

3. **SAE data review**
    a. Verbal Update - For each new patient, a description of the past and current medical history, concurrent medication
    b. Verbal Update - For each patient, new/unresolved AEs (patient, dose cohort, AE, CTC grade, drug interruption if relevant, change in dose if relevant, any other comments)
    c. Verbal Update - New SAEs (above plus description of SAE and how managed)

4. **PK report**

Report will be provided following the attached template. The transfer, analysis and production of the PK data and the report will be scheduled to occur in alignment with the SRC dose escalation meetings and will not be required for the regular scheduled SRC meetings.

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