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Bipolar Androgen Therapy Plus Olaparib in Patient with Castration-Resistant Prostate Cancer

Financial and Medication Support: AstraZeneca

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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
ADT	Androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	Androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAT	Bipolar Androgen Therapy
BD/BID	Twice daily
CI	confidence interval
CL	clearance
C_{max}	peak concentration
$C_{max,ss}$	peak concentration at steady state
C_{min}	trough concentration
$C_{min,ss}$	trough concentration at steady state
CNS	central nervous system
CR	complete response
CRPC	Castration-resistant prostate cancer
CT	computed tomography
CTC	circulating tumor cell
ctDNA	cell-free tumor DNA
DDR	DNA Damage Repair
DHEA-S	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

Abbreviation or special term	Explanation
DSB	Double strand DNA break
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
FFPE	formalin fixed paraffin embedded
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HR/HRR	Homologous recombination/Homologous Recombination Repair
HRD	Homologous recombination deficiency
ICF	informed consent form
ICH	International Conference on Harmonization
IF	Immunofluorescence
IHC	immunohistochemistry
IRB	Institutional Review Board
IV	intravenous(ly)
LHRH	luteinizing hormone releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHEJ	Non-homologous end-joining
OR	objective response
ORR	objective response rate
OS	overall survival
PC	Prostate cancer
PCWG	Prostate Cancer Working Group
PFS	progression-free survival
PK	pharmacokinetic(s)

Abbreviation or special term	Explanation
PR	partial response
PRO	patient-reported outcome
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SPT	Supraphysiologic Testosterone
SSB	Single strand DNA break
SUSAR	suspected unexpected serious adverse reaction
T	Testosterone
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to peak concentration
$T_{max,ss}$	time to peak concentration at steady state
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
WHO	World Health Organization

1. INTRODUCTION

Shortly after Charles Huggins first reported on the remarkable palliative benefits of androgen deprivation therapy (ADT) in men with advanced prostate cancer, case series recounting the paradoxical benefits of testosterone (T) supplementation in prostate cancer patients began to emerge [1-5]. Recent preclinical studies have shed light on the mechanisms underlying the antitumor effects of androgens, and have renewed our interest in exploring high-dose T as a therapeutic strategy for men with castration-resistant prostate cancer (CRPC) [6-10]. As such, we have recently published the results of a pilot study designed to evaluate the effects of rapid cycling between very high and very low serum T levels in men with asymptomatic CRPC, a mode of therapy we call bipolar androgen therapy (BAT) [11]. In this study we found that ~50% of men had PSA declines and radiographic responses (partial or complete responses). Because the induction of DNA damage appears to be a key mechanism underlying the clinical effects of BAT, we hypothesize that combining BAT with the PARP inhibitor olaparib to impair DNA damage repair (DDR) will improve clinical efficacy.

1.1 Disease Background

Prostate cancer is the second most common cause of cancer deaths in men in the US.[12] Approximately one in every six American men will be diagnosed with the disease during his lifetime. The disease continuum has been modeled as a series of states defined by the presence or absence of detectable metastases and whether testosterone levels are in the castrate or non-castrate range (Figure 1). Each state represents a significant milestone in the illness that forms the basis for clinical research and for medical decision making in the context of routine clinical practice. The standard treatment for patients with metastatic disease includes surgical or medical castration with a luteinizing hormone releasing hormone (LHRH) analog, which is continued indefinitely (i.e. androgen deprivation therapy, ADT). The results are predictable, with a decline in PSA followed by tumor regression, a period of stability in which the tumor does not proliferate and PSA remains stable, followed by rising PSA and regrowth as a castration resistant lesion. Prostate cancer progression despite castrate levels of testosterone represents a transition to a lethal disease phenotype referred to as castration-resistant prostate cancer (CRPC).

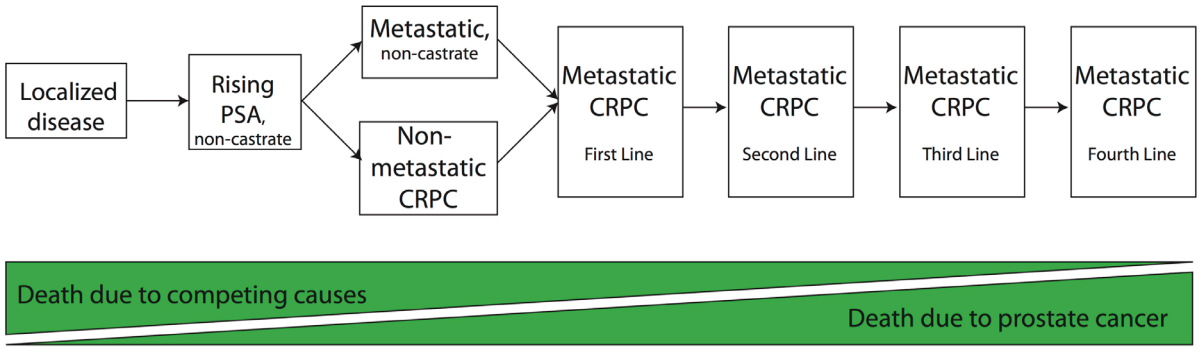

Figure 1. Clinical states of prostate cancer.

Since 2004 there have been six FDA approved agents for the treatment of metastatic CPRC (mCRPC), all on the basis of Phase III data demonstrating a modest survival benefit compared to controls (median overall survival advantage approximately 2 to 5 months) (Figure 2).[13-21]. The first agent, docetaxel, is a semi-synthetic taxane that function by inhibiting microtubule activity. Originally it was only indicated for men with mCRPC, but recent data has demonstrated that it is highly effective when combined with ADT in the upfront treatment of metastatic hormone-sensitive prostate cancer.[18, 21-24] In 2010, the next-generation taxane cabazitaxel was also approved for use in patients progressing on docetaxel.[15]

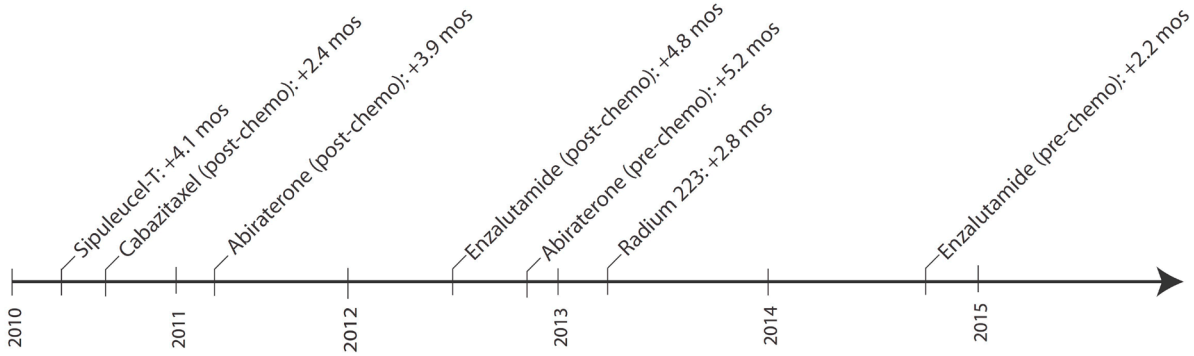

Figure 2: Timeline of recent Food and Drug Administration (FDA) approval for mCRPC drugs. Median improvement in overall survival in months (mos) is provided.

More recently, it has become apparent that the androgen receptor (AR) signaling axis remains engaged even in the castration-resistant setting, with AR-regulated genes (e.g. *PSA*) often expressed at high levels[25]. While older literature had described CRPC as a 'hormone refractory' disease state, the term 'castration-resistant' has been adopted largely due to the increasing recognition that androgen receptor (AR) signaling still plays a vital role in driving prostate cancer growth, and remains a viable target in the CRPC disease space.[26] Indeed, the development of newer drugs like abiraterone (an extragonadal inhibitor of androgen biosynthesis) and enzalutamide (a pure AR-antagonist) that function to inhibit ligand-AR interaction have provided proof of principle that the AR remains an important driver of CRPC growth [13, 14, 19, 20].

Given their similar mechanisms of action, it is not surprising that evidence of cross-resistance between abiraterone and enzalutamide has begun to emerge, with overexpression of AR representing the most frequently observed mechanisms of resistance to AR-signaling inhibitors [25, 27-35]. Other resistance mechanisms described, include: increased extragonadal androgen synthesis; the emergence of constitutively active AR splice variants (AR-Vs); AR point mutations; AR-signaling activation via alternative pathways (e.g. AKT/mTOR/Pi3K, HER kinases); and activation of other nuclear hormone receptors such as the glucocorticoid receptor[25, 36-45]. One or more of these mechanisms may provide a basis for why progression on one AR-directed agent may portend a poor response to the other drug when used second line.

The other two agents approved for mCRPC are sipuleucel-t and radium-223. Sipuleucel-T is an *ex vivo* autologous immunotherapy product and remains the only cancer vaccine shown to improve overall survival in Phase III testing [16, 46]. It is designed to produce an immune response toward the prostate antigen PAP. Interestingly no difference in disease progression was observed between patient receiving sipuleucel-t or placebo in the Phase III study, nor did it associate with tumor or PSA responses. Sipuleucel-t is not approved for patients with symptomatic disease, and given that only men with a life expectancy ≥6 months were included in the pivotal Phase III trial, it is not appropriate for patients with rapidly progressive disease or those expected to live <6 months. Radium-223 is a novel alpha emitting radiopharmaceutical that possesses intrinsic bone targeting properties similar to that of other alkaline earth elements, such as calcium, and is approved for the treatment of symptomatic, bone-metastatic CRPC. Radium-223 is not expected to affect soft tissue metastases, and on this basis radium-223 is not indicated for patients with visceral metastases or nodal metastases >3 cm[17].

As outlined above, the majority of the agents approved for mCRPC are either AR-signaling inhibitors (i.e., abiraterone and enzalutamide), only indicated for a narrow subset of patients, or have minimal clinical efficacy. Approaches that do not rely on *inhibiting* the AR-signaling axis are sorely needed. Importantly, preclinical studies have demonstrated that high-dose testosterone has potent anti-tumor activity in prostate cancer models with high AR levels – indicating that treatment with androgen supplementation is likely to be most effective in advanced prostate cancer patients who have progressed on drugs that inhibit AR-signaling[6, 47]. In addition, recent mechanistic studies have indicated that high-dose testosterone may exert an antitumor effect by inducing double strand DNA (dsDNA) breaks, providing a rationale for combining high-dose testosterone with agents that can impair DNA repair (e.g. PARP inhibitors).

1.2 Supraphysiologic Testosterone (SPT) in CRPC Background

1.2.1 SPT in CRPC Pre-clinical experience

As prostate cancer cells adapt to low androgen levels, one of the most frequently observed events is an adaptive upregulation of the androgen receptor (AR) – likely driving resistance to AR-signaling inhibition [25, 35]. We hypothesized that the adaptive autoregulation of AR may serve as a therapeutic liability, sensitizing prostate cancer cells to supraphysiologic androgen-induced cell death. In support of this, we and others have observed that adapted prostate cancer cell lines display blunted cell growth when exposed to supraphysiologic androgen levels (Figure 3) [7, 11, 47-52].

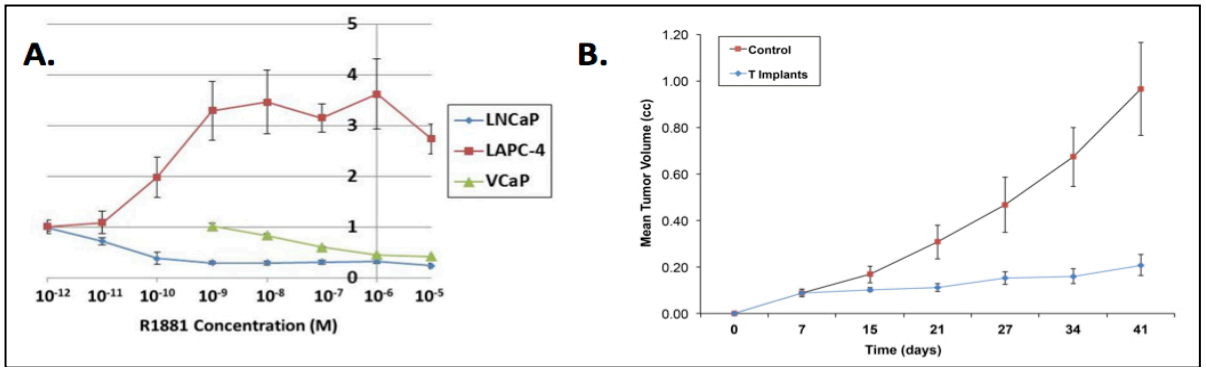

Figure 3: Growth inhibitory effects of supraphysiologic androgens. LNCaP, LAPC-4 and VCaP cells were adapted to grow in charcoal-stripped media. After demonstrating castrate-resistant growth, cells were exposed to supraphysiologic levels of androgens. **A)** R1881 dose response. Y-axis is fold change in cell number compared to day 0 control after 5 days of exposure. **B)** Growth of adapted LNCaP cells in nude mice treated with a testosterone implant (sq) vs an empty (control) implant ($P < 0.05$ after day 21).

Studies exploring the mechanisms behind the paradoxical antitumor effects of SPT have demonstrated that in high-AR cell lines, rapidly transitioning from a castrate to high androgen environment induces double strand DNA (dsDNA) breaks, an effect likely mediated by topoisomerase IIB (TOP2B) [6, 10, 11]. As AR-mediated transcription proceeds, knots and tangles in DNA occur. In order to overcome these topologic constraints, TOP2B induces transient dsDNA breaks, which are then repaired by the enzyme. Supporting this model is preclinical data showing that the TOP2B poison etoposide is able to potentiate dsDNA breaks by inhibiting DNA re-ligation (Figure 4) [11]. Furthermore, *in vivo* experiments demonstrate synergy when SPT is combined with DNA damaging doses of radiation [53].

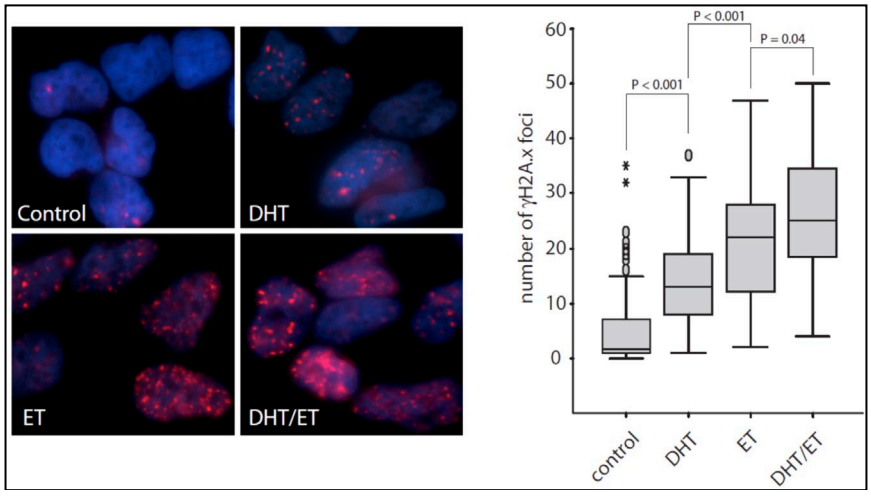

Figure 4: Supraphysiologic androgens induce dsDNA breaks in prostate cancer cells. γ-H2A.x foci in LNCaP cells after exposure to 100 nM DHT or 100 mM etoposide or the combination.

1.2.2 SPT in CRPC Clinical experience

The aforementioned preclinical work exploring the paradoxical growth inhibitory effects of androgens in high AR expressing prostate cancer cell lines renewed our interest in exploring high-dose T as a therapeutic strategy for men with mCRPC [6-10]. As such, we developed a form of intermittent high-T therapy we termed Bipolar Androgen Therapy (BAT) in which serum T levels are rapidly cycled between very high and very low levels in men with asymptomatic mCRPC.[11] We hypothesized that BAT would prevent AR levels from adapting to either high or low androgen conditions, thereby preventing the emergence of resistance to high-dose T. In addition, because studies have shown that the dsDNA breaks and apoptosis induced by high-doses of androgens are transient, rapid cycling of T could result in repeated rounds of DNA damage, enhancing antitumor effects [53].

Clinically, BAT has been administered as intramuscular (IM) injections of either testosterone enanthate or cypionate (which have identical pharmacokinetics) at a dose of 400 mg every 28 days. This dose and formulation was selected because it has been shown to drive T levels well into the supraphysiologic range (>1500 ng/dL), followed by a rapid decline in T back to the near-castrate range at the end of a 28 day cycle [11, 54].

In our initial pilot study testing BAT, we treated 16 CRPC patients with BAT combined with etoposide for 3 months. Patients whose PSA was falling at the end of this 3 month period were allowed to continue on BAT monotherapy until disease progression. In total, 14 patients completed the first 3 months of therapy and were response evaluable. Of these 14 men, we observed high response rates, with robust PSA responses **(**Figure 5A**)** and tumor shrinkage on scans in 50% of patients [11]. In a more recent study testing BAT in men with hormone-sensitive prostate cancer (HSPC) we found that BAT resulted in high-rates of PSA suppression and importantly also in improvements in quality of life (Figure 5B)[55]. Preliminary results from the RESTORE trial, a Phase II study testing BAT in men progressing on enzalutamide (N=30), have also revealed evidence of clinical activity in heavily pre-treated mCRPC. In that study 30% of patients had PSA declines ≥50% from baseline and a median clinical/radiographic PFS of 8.6 months was observed, which compares favorably to other AR-directed therapies given post-enzalutamide [56, 57]. Importantly, BAT was found to be well tolerated across the three trials evaluating it in men with advanced prostate cancer (Figure 6).

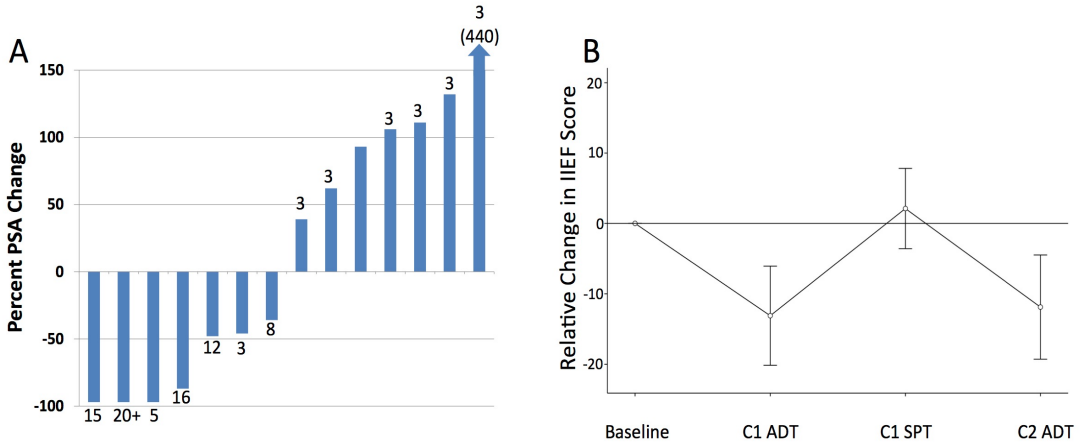

Figure 5. (A) Waterfall Plot Showing Max PSA Change relative to baseline in the pilot BAT study. The number at the end of each bar indicates the number of treatment cycles received. Number in parentheses indicates percent PSA change in a case where the bar was truncated. **(B)** Mean change in quality of life (QoL) from baseline (based on IIEF survey) in men with hormone sensitive PC receiving BAT. Increasing values indicate improved QoL. C1, cycle 1; C2, cycle 2.

BAT Pilot Study (N = 16) [11]				RESTORE (N = 30) [68]			BATMAN (N = 29) [67]	
Adverse Event	**Grade 1-2 N (%)**	**Grade 3-4 N (%)**	**Any Grade N(%)**	**Adverse Event**	**Grade 1-2 N (%)**	**Grade 3-4 N (%)**	**Adverse Event**	**Grade 1-2 N (%)**
Anemia	3 (18.8)	0	3 (18.8)	Breast sensitivity	5 (17)		Hot Flashes	15 (52)
Dysgeusia	3 (18.8)	0	3 (18.8)	Pulmonary embolism		1 (3)	Edema	11 (38)
Weight gain	3 (18.8)	0	3 (18.8)	Musculoskeletal pain	12 (40)		Weight Gain	4 (14)
Anorexia	4 (25)	0	4 (25)	Elevated hemoglobin	11 (37)		Fatigue	3(10)
Breast sensitivity	4 (25)	0	4 (25)	Rash	5 (17)		Pain	2 (7)
Neutropenia	3 (18.8)	1 (6.3)	4 (25)	NSTEMI		1 (3)	Hematuria	2 (7)
Edema	8 (50)	0	8 (50)	Urinary obstruction		1 (3)	Tinnitus	1 (3)
Alopecia	9 (56.3)	0	9 (56.3)	Pain	2 (7)		Mood Changes	1 (3)
Fatigue	9 (56.3)	0	9 (56.3)				Loss of Libido	1 (3)
Nausea	10 (62.5)	0	10 (62.5)				Insomnia	1 (3)
Pulmonary embolism	0	2 (12.5)	2 (12.5)				Heart Palpitations	1 (3)
Death	0	1 (6.3)	1 (6.3)				Facial Flushing	1 (3)
							Dyspnea with exertion	1 (3)
							Anxiety	1 (3)

Figure 6. Adverse events observed in trials testing BAT in men with advanced prostate cancer. Note, the BAT Pilot Study tested BAT in combination with etoposide for the first 3 months of treatment. One individual developed neutropenic sepsis and subsequently died. This was deemed to be a consequence of etoposide and unrelated to BAT.

Compared to our experience with BAT, older studies testing *physiologic* doses of T in men with CRPC have documented modest benefit at best [58, 59]. In these contemporary Phase I studies testing physiologic doses of T in men with CPRC, there were no objective radiographic responses and PSA declines >50% occurred in only one out of 27 patients [58, 59]. This is in contrast to our trials testing intermittent doses of SPT (i.e., BAT), where we observed high response rates in men with CRPC, with robust PSA responses and tumor shrinkage in 50% of patients [11].

Clinical Evidence for BAT Inducing DNA Damage

Recently, a case report was published that described an extreme responder to BAT who harbored deleterious *ATM* and *BRCA2* mutations. Because this individual's tumor had an intrinsic deficiency in its ability to repair DNA damage, it was hypothesized that dsDNA breaks induced by high-dose T were unable to be repaired, and BAT was therefore synthetically lethal to tumor cells[60]. As part of ongoing translational work aimed at understanding the drivers of response/resistance to BAT, we have performed next-generation sequencing on tumor DNA from seven patients receiving BAT on the TRANSFORMER clinical trial, which is testing BAT *vs.* enzalutamide in mCRPC patients who have progressed on abiraterone [clinicaltrials.gov: NCT02286921]. Consistent with the findings from the aforementioned case report, we have found that the majority of patients exhibiting a PSA response have detectable alteration in DNA damage repair pathway genes – further supporting the induction of DNA damage as a key mechanism driving clinical responses to BAT (Figure 7).

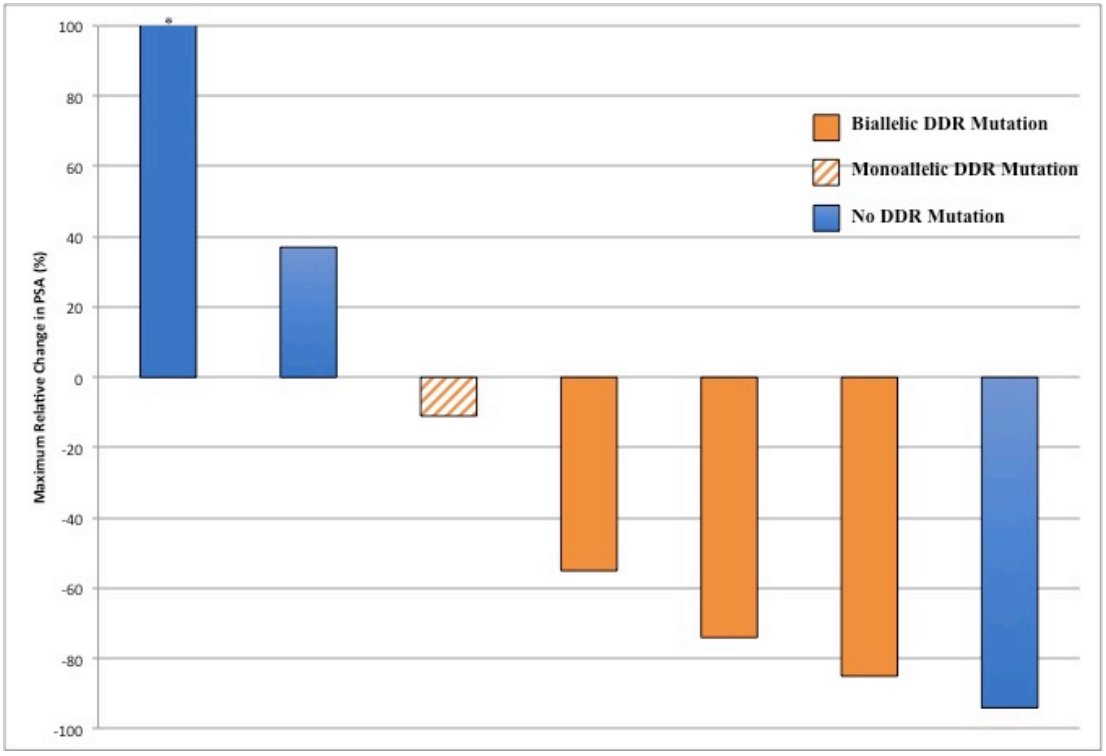

Figure 7: Percent change in PSA compared to baseline in men receiving Bipolar Androgen Therapy. DDR = DNA damage response; * = truncated at 100% increase in PSA above baseline.

1.3 Olaparib Background

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

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

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication [61-64]. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates [64-66]. In addition, PARP is involved in repairing DSB through the alternative non-homologous end-joining (NHEJ) pathway, and PARP inhibitors could therefore further impair DSB repair in HR-deficient tumors[67-69]. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models *in vivo* and in the clinic [70-72]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair [73, 74]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. In addition, PARP inhibitors have been shown across multiple preclinical tumor models to potentiate the antitumor effects of DNA damaging cytotoxic agents (e.g. alkylating agents, platinum chemotherapy) as well as radiation [72, 75-78]. Importantly, many of these studies have shown that the observed anti-tumor effects are not restricted to cell lines with loss of HR pathway genes.

1.3.1 Pre-clinical experience

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

A range of tumor cell lines have been investigated using colony formation assays for sensitivity to PARP inhibition with olaparib as a single agent. IC50 data were calculated for each cell line across KU95, a mixed tumor type panel of 95 cancer cell lines that also contained ovarian cancer cell lines (Figure 8). Cell lines representing breast, ovarian, colorectal, head and neck, lung and pancreatic tumor types were screened and shown to have wide-ranging cellular activity from the low nM (IC50 18 nM) to in excess of 10 μM (cell lines with IC50 greater than 10 μM, the top concentration used, where an exact IC50 could not be determined, are listed as 10 μM with a zero Sd for plotting purposes).

Cell lines with known inactivating *BRCA1* or *BRCA2* mutations, *BRCA1* promoter methylation or other DNA repair defects e.g., Meiotic Recombination 11 (*MRE11*; *MRE11A*), were also included. The panel was also profiled for relative protein and messenger ribonucleic acid gene expression levels of key DNA damage response (DDR) and HRR associated genes such as *BRCA1*, *BRCA2*, *ATM*, *ATR*, mediator of DNA damage checkpoint protein 1 and *MRE11A*.

A cell line was classified as HRD when either relative gene or protein expression for 2 or more HRR target genes was less the half (50%, 0.5) relative to the mean expression. Cell lines with published literature confirming deleterious, homozygous loss-of-function *BRCA1* or *BRCA2* mutations were also classed as HRD [79-82].

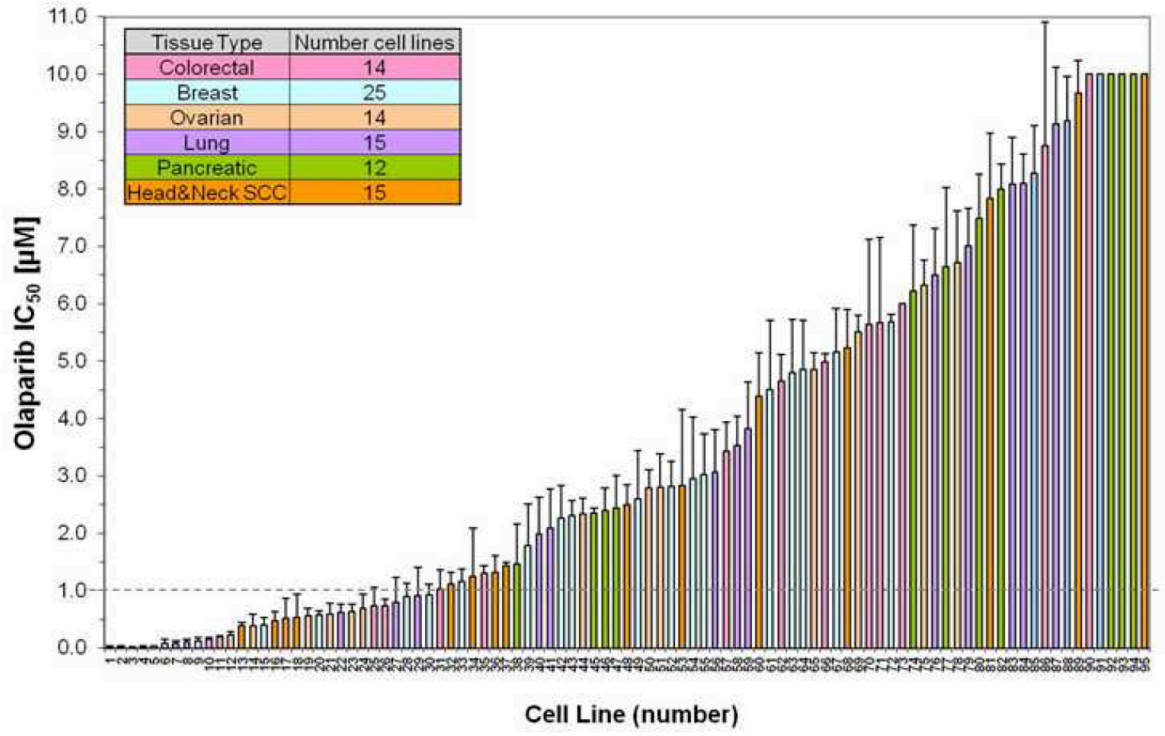

Figure 8: Graphical plot of olaparib activity (IC_{50}) across the KU95 cell line panel.

While a broad range, continuum of growth inhibitory (IC_{50}) activity for olaparib was observed across the cell line panel (ranging from 0.018 µM through to >10 µM), associations with enhanced olaparib sensitivity (IC_{50} <1 µM) were observed in cell lines with known *BRCA1* or *BRCA2* mutations or low expression of HRR genes/proteins (Figure 9. These data are consistent with the proposed mechanism of action of PARP inhibitors, where deficiencies in HR lead to an inability to repair DNA DSBs resulting from PARP inhibitor treatment. While there is a clear enrichment for HRD within the most sensitive cell lines (24/30), there are still responsive cell lines for which a molecular basis has not yet been ascribed.

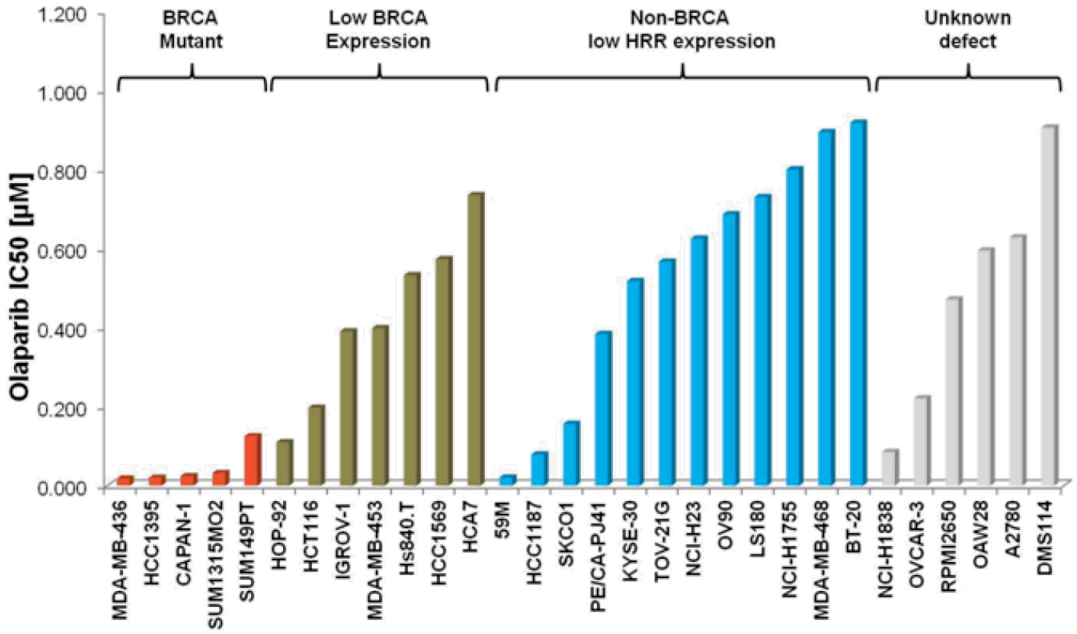

Figure 9: Graphical plot of olaparib sensitive cell lines (IC50 <µM) arranged by known BRCA1/2 mutation status or low expression of HRR genes.
Plot of highly olaparib sensitive cell lines (IC_{50}<1 µM) clustered by the presence known deleterious *BRCA1/2* mutations (*BRCA* mutant), low BRCA1/2 expression (low BRCA expression), low expression of 1or more HR genes in the absence of *BRCA1/2* mutation/low expression (non-BRCA, low HRR expression) or those without any of these defects (unknown defect).

Similarly, *in vivo* orthotopic *BRCA* knockout models testing olaparib showed marked anti-tumor effects. In both a *BRCA1*-/- orthotopic mouse mammary tumor model and a *BRCA2*- /- orthotopic mouse model, dosing with 50 mg/kg olaparib once daily (od) for 28-days showed significant anti-tumor efficacy for single agent olaparib [71, 72].

An analysis of the correlation of olaparib response with several standard-of-care chemotherapies in a panel of breast cancer cell lines demonstrated a strong correlation with both carboplatin (0.84, p=0.0006) and camptothecin (0.8, p=0.0018). This is consistent with what is known about the types of DNA damage they induce (intra-strand and inter-strand cross-links for platinum and trapped topoisomerases-DNA adducts for camptothecins, both of which result in DNA DSB formation in replicating cells) and the DDR pathways that deal with them (primarily HRR in cells undergoing DNA replication). The same does not hold for a mechanistically unrelated chemotherapy, such as paclitaxel (-0.11) whose mechanism of action is unrelated to the induction of DNA damage.

An analysis of olaparib and platinum response across several tumor cell lines indications where platinum treatment is standard-of-care and included ovarian, non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma cell lines. Consistent with the breast cancer cell line data, the strong correlation between platinum response and olaparib response was observed both *in vitro* (Figure 10) and *in vivo*.

When olaparib is combined with the mono-methylating agent TMZ, potentiation of its anti-tumor activity across a number of cancer cell lines is observed. Moreover, other PARP inhibitors have also been shown to be effective with a number of non-classical alkylating agents including MMS, DTIC and TMZ. However, for the "classic" alkylating agents such as cyclophosphamide and N, N'-bis(2-chloroethyl)-N-nitrosourea (BCNU; carmustine) only some early literature reports are available on showing potentiation but, to date, no data have been generated for olaparib with such agents. Similarly, the effectiveness of olaparib with topoisomerase I inhibitors (i.e., camptothecin family) and platinum agents (e.g., cisplatin and carboplatin) has been shown in both *in vitro* and *in vivo* studies.

1.3.2 Toxicology and safety pharmacology summary

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

In repeat dose oral toxicity studies of up to 6 months duration in rats and dogs, the principal target organ for toxicity was the bone marrow, with associated changes in peripheral hematology parameters, which may be related to the primary pharmacology of olaparib. All changes showed full or partial recovery following withdrawal of olaparib.

Olaparib was not mutagenic in an Ames bacterial mutation test, but was clastogenic in a CHO chromosome aberration test in vitro. When dosed orally, olaparib also induced micronuclei in bone marrow of rats. These findings are consistent with genomic instability resulting from the primary pharmacology of olaparib.

In reproductive toxicology studies in rats, oral dosing of olaparib prior to mating produced no adverse effects on male fertility. In female rats, although conception rates were unaffected by pre- and peri-conception dosing, embryofetal survival was decreased. Administration of olaparib during organogenesis had an adverse effect on embryofetal survival and also increased major fetal malformations at dose levels that were not maternally toxic. The effects on embryofetal development are considered to be related to the primary pharmacology of olaparib.

Exposures in the repeat dose and reproductive toxicology studies were below those achieved at the clinical therapeutic doses of 400 mg bd olaparib (capsule) and 300 mg bd (tablet).

Combination studies in rats suggest potential for olaparib to exacerbate the effects of TMZ and topotecan, although combination of olaparib with these anti-cancer agents did not induce any additional target organ toxicities to those seen with single agent administration.

Monotherapy

Data from the development program indicate that olaparib is generally well tolerated at monotherapy doses up to 400 mg bd (capsule formulation) and 300 mg bd (tablet formulation) in patients with solid tumors. Administration of olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation.

Combination studies

Studies of olaparib in combination with various chemotherapy agents indicate an increase in bone marrow toxicity (anemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. The effects are generally transient but treatment delays are common and alternative administration schedules/toxicity management processes have been evaluated within some of these studies. When this type of toxicity has occurred it has been managed by routine clinical practice including dose delays, dose reductions, intermittent dosing and/or the use of supportive care measures, including G-CSF.

1.3.3 Clinical experience

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

1.3.3.1 Olaparib in mCRPC

Failure to accurately repair DNA damage can lead to the accumulation of mutations, and an increased cancer risk [83, 84]. Not surprisingly, mutations in DNA repair genes have been associated with several cancer predisposition syndromes [85-87]. It has also been shown across a variety of malignancies that when DNA damage repair deficiency occurs – often as a result of homozygous loss of function mutations in *BRCA 1/2*, *ATM* and other genes involved in homologous recombination – alternative DNA repair mechanisms are required to prevent genomic instability and cell death. Poly (ADP-ribose) polymerase (PARP) has been shown to be a key mediator in this respect. As such, strategies to inhibit PARP activity have been shown to be effective in a number of cancers with impaired homologous recombination [70, 88-91]. In addition, more recent data has shown that PARP inhibition may be an effective strategy to augment the antitumor effects of other DNA damaging agents (e.g. alkylating and platinum chemotherapies) in cancers with intact DDR pathways [91, 92].

As part of our participation in the SU2C/AACR/PCF Prostate Cancer Dream Team, we have found that ~20% of CRPC patients harbor biallelic loss of a DNA damage repair (DDR) pathway gene [35]. In addition, more recent studies from our group have demonstrated that in men with metastatic prostate cancer, there is a high incidence (~12%) of deleterious alteration in DDR genes [87]. This data provides a strong rationale for a precision oncology approach to treating advanced prostate cancer with drugs that impair DDR (e.g. PARP inhibitors). Proof of concept for this approach is derived from the TOPARP Trial [88]. This was a Phase II study testing olaparib 400 mg by mouth twice daily in men with metastatic CRPC. The primary endpoint was response rate, which was defined as either an objective radiographic response per RECIST criteria v1.1, a PSA reduction of ≥50% from baseline (i.e., PSA_{50} response) or a confirmed reduction in circulating tumor cells (CTCs) from ≥5 cells per 7.5 mL of blood to <5 cells per 7.5 mL of blood. Fifty patients were enrolled, and all were post-docetaxel. Forty-nine patients received prior abiraterone or enzalutamide. Sixteen patients (33%) met the primary endpoint. Responses to olaparib were enriched in the subset of patients with homozygous deletions, deleterious mutations, or both in DDR genes (e.g. *BRCA1/2*, *ATM*, Fanconi's anemia genes, and *CHEK2*) (Figure 10). In this cohort, response rate was 88%. The observed safety profile of olaparib was consistent with that observed in other solid tumor trials. On the

basis of this trial, larger randomized studies have been launched to further evaluate PARP inhibitors in men with CRPC.

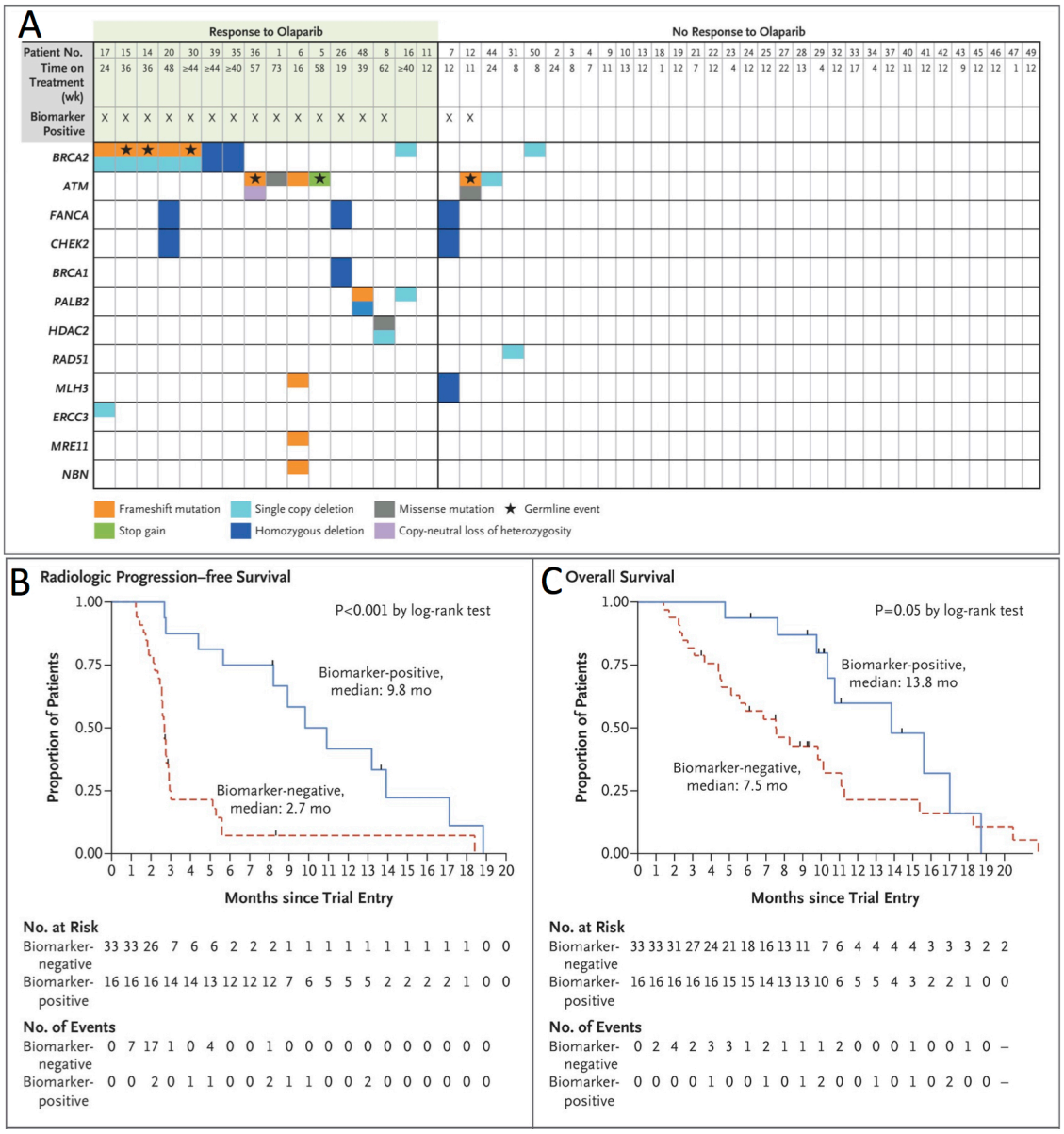

Figure 10: Results from the Phase II TOPARP Trial [88]. Patients with metastatic, castration-resistant prostate cancer were treated with olaparib tablets at a dose of 400 mg twice a day. **(A)** Responses to olaparib were enriched in patients with biallelic loss of DNA repair genes. Radiographic PFS **(B)** and overall survival **(C)** were significantly longer in patients with biallelic loss of DNA repair genes (i.e., biomarker-positive).

In 2020, olaparib was approved as treatment for mCRPC patients who have progressed on prior abiraterone or enzalutamide on the basis of the Phase III PROfound study[93]. PROfound was a randomized, open-label study evaluating olaparib vs. physician's choice of

enzalutamide or abiraterone in men with mCRPC and deleterious germline or somatic mutations in HR repair genes. Enrollment was allowed on the basis of a panel of genes involved in the HR repair pathway. The primary endpoint was progression free survival (PFS) in the group with *BRCA1*, *BRCA2* and/or *ATM* mutations (Cohort A). A second cohort consisted of patients with mutations in other HR repair-associated genes (Cohort B). Secondary endpoints were analyzed in a hierarchical fashion to control for trial-wide type 1 error associated with multiple testing, which occurred in the following order: objective response rate (Cohort A), PFS (combined Cohorts A and B), time to pain progression (Cohort A), and overall survival (Cohort A).

The primary endpoint was met, with a PFS of 7.4 months vs. 3.6 months (P<0.001) in the olaparib vs. control groups for Cohort A. Secondary endpoints also favored the olaparib group, with an objective response rate in Cohort A of 33% vs. 2% in control group (P<0.001), median PFS of 5.8 months vs. 3.5 months for combined Cohorts A and B (P<0.001), median overall survival of 18.5 months vs. 15.1 months for Cohort A (P=0.02) and median overall survival of 17.5 months vs. 14.3 months for combined Cohorts A and B (P=0.0063). These results led the FDA to approve olaparib for mCRPC patients with somatic or germline alterations in *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and/or RAD54L.*

Of note, PARP inhibitors have also been shown across multiple preclinical tumor models to potentiate the antitumor effects of DNA damaging cytotoxic agents (e.g. alkylating agents, platinum chemotherapy) as well as radiation [72, 75-78]. Importantly, these effects were not restricted to cell lines with biallelic loss of DNA damage pathway genes. Proof of concept for combining PARP inhibitors with DNA damaging agents is provided by the I-SPY 2 TRIAL. This study was a multi-center, randomized, Phase II “platform” trial testing multiple experimental regimens added to a control “backbone” regimen. Patients with high-risk primary breast cancer planning to undergo surgery were eligible to receive neoadjuvant therapy per protocol [89]. The control arm consisted of 12 weekly cycles of paclitaxel followed by 4 cycles, every 2-3 weeks of doxorubicin plus cyclophosphamide. One of the experimental arms combined the PARP inhibitor veliparib 50 mg by mouth twice daily and carboplatin AUC 6 concurrently with the weekly paclitaxel. The primary endpoint was pathologic complete response (pCR) rate as assessed at the time of surgery. In the subset of patients with triple negative breast cancer (i.e. HER2 negative, ER/PR negative), the estimated rate of pCR was 51% (95% Bayesian probability interval [PI], 36 to 66%) in the veliparib-carboplatin arm compared to 26% (95% PI, 9 to 43%) in the control group. This translated to an 88% predicted probability of success in the Phase III setting. Importantly, this study was not restricted to patients with loss of DNA repair pathway genes, however, it was noted that more patients in the veliparib-carboplatin arm (12/72, 17%) had deleterious mutations in *BRCA1* or *BRCA2* compared to control (2/44, 5%). Several other studies testing olaparib in combination with DNA damaging therapies are underway or have recently completed. The results of these studies generally support combining PARP inhibitors with DNA damaging

therapies. Further details on these trials can be found in the Investigator's Brochure (Section 5.2.2: Efficacy: combination studies).

1.3.3.2 Emerging Safety Profile

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

The safety profile is based on pooled data from 2901 patients with solid tumors treated with olaparib monotherapy in clinical trials at the recommended dose.

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

Table 1: Adverse Drug Reactions reported in Clinical Trials

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (All CTCAE grades)	Frequency of CTCAE Grade 3 and above
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Myelodysplastic syndrome/acute myeloid leukemia	Uncommon	Uncommon
Blood and lymphatic system disorders	Anemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Very common	Common
	Lymphopenia[a]	Common	Uncommon
Immune system disorders			
	Hypersensitivity[a]	Uncommon	Rare
	Angioedema [b]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnea[a]	Very common	Common
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhea	Very common	Common
	Nausea	Very common	Common
	Dyspepsia	Very common	-
	Stomatitis[a]	Common	Uncommon

	Upper abdominal pain	Common	Uncommon
Skin and subcutaneous tissue disorders	Rash[a]	Common	Rare
	Dermatitis	Uncommon	-
	Erythema nodosum[b]	Rare	-
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Uncommon
	Mean cell volume increased	Uncommon	-

[a] Anaemia includes preferred terms (PTs) of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased haemoglobin decreasednormocytic anaemia and red blood cell count decreased; Cough includes PTs of cough and productive cough; Dermatitis includes PTs of dermatitis and dermatitis allergic; Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity;; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Lymphopenia includes PTs of lymphocyte count decreased, and lymphopenia ; Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased; Rash includes PTs of exfoliative rash, generalised erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic;; Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis. Thrombocytopenia includes PTs of platelet count decreased, and thrombocytopenia.

[b] Observed in the post-marketing setting.

CIOMS=Council for International Organization of Medical Sciences; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; PT = Preferred term; SOC=System organ class. MedDRA version 22.1

Description of selected adverse reactions

Myelodysplastic syndrome/acute myeloid leukaemia

In clinical studies, across all indications, MDS/AML occurred uncommonly in patients on treatment and during the 30-day safety follow up, and <1.5% at any time after starting olaparib, including cases actively solicited during the long term follow up for overall survival. In patients with BRCAm platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with olaparib treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8% in patients receiving olaparib and 4% in patients receiving placebo at a follow-up of 5 years. In the olaparib arm, 9 out of 16 MDS/AML cases occurred after discontinuation of olaparib during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the olaparib arm and late onset of MDS/AML. The risk of MDS/AML remains < 1.5% at 5 year follow up in the first-line

setting when olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years.

Hematological toxicity

Anaemia and other haematological toxicities are generally low grade (CTCAE Grade 1 or 2) however, there are reports of CTCAE Grade 3 and higher events. Anaemia was the most common CTCAE Grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with olaparib monotherapy the incidence of CTCAE Grade ≥2 shifts (decreases) from baseline in haemoglobin was 23%, absolute neutrophils 19%, platelets 6%, lymphocytes 29% and leucocytes 20% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment with olaparib, and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.

Other laboratory findings

In clinical studies with olaparib the incidence of CTCAE Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 11%. Data from a double-blind placebo controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. The increase in blood creatinine level might be explained by inhibition of renal transporters such as OCT2, MATE1 and MATE2K by olaparib, as blood creatinine levels were found to return to baseline after treatment discontinuation. 90% of patients had creatinine values of CTCAE Grade 0 at baseline and 10% were CTCAE Grade 1 at baseline.

Nausea and vomiting

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

Combination studies

Safety data from studies in which olaparib has been administered in combination with other agents are discussed in the Investigator's Brochure. The degree of bone marrow suppression observed in some patients in the combination studies has however been greater than would be

expected with the chemotherapy agent alone, as per label information. Myelotoxicity has been observed in studies evaluating olaparib with the following combination therapies: DTIC; carboplatin; paclitaxel; carboplatin + paclitaxel; gemcitabine; topotecan; cisplatin; doxorubicin, cisplatin + gemcitabine; or irinotecan.

The principal hematological toxicities observed have been neutropenia, thrombocytopenia and anemia. These findings are consistent with pre-clinical findings [72, 76-78, 94].

Adverse events of special interest

Myelodysplastic syndrome/acute myeloid leukemia

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

New Primary Malignancies other than MDS/AML

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

Pneumonitis

Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When olaparib was used in clinical studies in combination with other therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or abnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.

1.4 Research hypothesis

We hypothesize, that co-treatment with BAT and olaparib will result in high response rates, and that these responses will be most pronounced in the subset of patient with DNA damage repair deficiencies. Because most patients experience improvements in quality of life following treatment with high-dose testosterone, we expect combination olaparib plus BAT to be safe and well tolerated. In addition, because the DNA damaging effects of BAT are restricted to prostate cancer cells with high AR expression, this combination should be synthetically lethal to tumor cells and result in minimal toxicity to normal tissues.

1.5 Rationale for conducting this study

There is ample evidence to support testing BAT in combination with olaparib. Preclinical models have repeatedly shown that SPT is able to induce DNA damage, an effect that can be

augmented through inhibiting the ability of TOP2B to repair dsDNA breaks [6, 10, 11]. The antitumor effect of SPT also appears to be enhanced when combined with DNA damaging doses of radiation [53]. Further supporting the importance of DNA damage as it relates to the clinical effects of SPT, is the observation that mutations in DNA damage repair genes (e.g. *BRCA 1/2*, *ATM*) may predict for response to BAT. Combining BAT with the PARP inhibitor olaparib is expected to result in enhanced clinical activity because PARP inhibitors have (i) been shown to impair DNA damage repair, and (ii) to potentiate the effects of other DNA damaging therapies (e.g. platinum chemotherapy and radiation) [75, 89]. Olaparib monotherapy has also shown preliminary signs of efficacy in heavily pretreated mCRPC patients with biallelic loss of DNA damage repair pathway genes [88]. *Therefore, testing BAT in combination with olaparib is likely to be an effective clinical strategy.*

Both BAT and olaparib have already shown evidence of clinical efficacy in the Phase II setting. Therefore the primary objective of this study will to evaluate efficacy. This will be determined by assessing PSA response rates after 12-weeks of combination therapy, as recommended by the Prostate Cancer Working Group 3 (PCWG3) [95]. Because PARP inhibitors have been previously shown to potentiate the effects of other DNA damaging agents – independent of DNA damage repair gene mutation status – we expect olaparib will also potentiate the clinical effects of BAT, resulting in high response rates compared to historical controls. However, since both BAT and olaparib appear most effective in patients with biallelic loss of DNA damage repair genes, we anticipate that BAT plus olaparib combination therapy will also be most effective in this subset of patients. In order to explore the effects of BAT plus olaparib in men with DNA damage repair deficiency, we will require that 50% of the study cohort have biallelic loss of DNA damage repair genes previously reported to associate with response to olaparib in mCRPC patients [88].

1.6 Benefit/risk and ethical assessment

As stated above, BAT has been reported to have clinical activity in patients with mCRPC that is refractory to second-generation AR-signaling inhibitors (i.e., enzalutamide), and is currently being tested in an ongoing randomized Phase II trial in men post-abiraterone [clinicaltrials.gov: NCT0228692] [11, 56]. Because BAT likely inhibits tumor growth in high AR prostate cancer cells by inducing dsDNA damage, we expect that combining it with olaparib to impair DNA damage repair will potentiate the clinical effects of BAT – improving response rates compared to BAT monotherapy. If effective, patients enrolled to this study would benefit by receiving an effective combination therapy that is otherwise unavailable. Only patients with mCRPC post-abiraterone and/or enzalutamide will be enrolled to this study. Because standard treatment options in this group only afford a modest survival benefit (Figure 2), any potential risks associated with clinical trial participation (as opposed to pursuing standard therapy) are justified.

In contrast to chemotherapy, BAT carries minimal toxicity and is associated with improvements in quality (Figure 5B). Furthermore, because BAT-induced DNA damage is limited to cells with high AR expression, we anticipate that this combination will induce synthetic lethality in prostate cancer cells only – thus resulting in a favorable safety profile.

Similarly, olaparib monotherapy has also been shown to be well tolerated in patients with advanced solid tumors, including mCRPC patients.

2. STUDY OBJECTIVES

2.1 Primary objective

Determine the PSA_{50} response rate (i.e., percent of patients with a PSA decline of at least 50% below baseline) following 12-weeks of treatment with bipolar androgen therapy (BAT) plus olaparib in men with asymptomatic metastatic castration-resistant prostate cancer (mCRPC) who have progressed on abiraterone and/or enzalutamide.

2.2 Secondary objectives

1. Determine the percent of mCRPC patients achieving a radiographic response per RECIST 1.1 criteria following treatment with BAT plus olaparib.
2. Determine the radiographic progression free survival (PFS) in mCRPC patients treated with BAT plus olaparib using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases [95, 96].
3. Determine the PSA PFS rate according to PCWG3 criteria in mCRPC patients treated with BAT plus olaparib [95].
4. Determine the PFS (i.e. whichever occurs first: clinical, radiographic or PSA progression) in mCRPC patients treated with BAT plus olaparib.
5. Determine the overall survival in mCRPC patients treated with BAT plus olaparib.
6. Track changes in quality of life (QoL) as determined using the FACT-P and International Index of Erectile Function (IIEF) surveys.
7. Assess the incidence and severity of adverse events according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

2.3 Exploratory objectives

Correlative work will be conducted in order to better understand the biology underlying response and resistance to BAT plus olaparib in men with mCRPC. Serial blood samples and metastatic tissue will be obtained at baseline and upon progression. Examples of studies to be conducted may include, but are not limited to:

1. Evaluate for differences in response and PFS in patients with/without mutations in genes involved in homologous recombination.
2. Determine intratumoral androgen levels using liquid chromatography-mass spectrometry (LC/MS)
3. Assess for evidence of dsDNA breaks using γ-H2AX immunostaining on circulating tumor cells (CTCs) and metastatic tissue
4. Assess androgen receptor (AR) and AR splice variant (AR-V) transcript expression levels using qRT-PCR on CTCs
5. Assess androgen receptor (AR) and AR splice variant (AR-V) protein expression levels using immunostaining on circulating tumor cells (CTCs) and metastatic tissue

6. Sequence tumor DNA (cell-free circulating tumor DNA [ctDNA] and/or metastatic tissue)
7. Conduct transcript profiling studies on CTCs (multiplexed qRT-PCR) and metastatic tissue (RNA-seq)

3. PATIENT SELECTION CRITERIA

Number of patients: 30 response evaluable mCRPC patients that have progressed on abiraterone and/or enzalutamide will be recruited from the Seattle Cancer Care Alliance/University of Washington Medical Center (SCCA/UWMC) genitourinary oncology clinic.

Number of centers: One.

3.1 Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:

1. Must be willing to provide informed consent prior to any study specific procedures

2. Age ≥ 18 years.

3. Documented histologically confirmed adenocarcinoma of the prostate.

4. Patient must have evidence of castration resistant prostate cancer as evidenced by PSA progression (per Prostate Cancer Working Group 3 [PCWG3] criteria) and a castrate serum testosterone level (i.e., ≤ 50 mg/dL) [95].

5. PSA must be at least 1 ng/ml and rising on two successive measurements at least two weeks apart.

6. Patients must have progressed on abiraterone and/or enzalutamide. There must be at least a 3-week washout period after stopping the most recent approved therapy for mCRPC (i.e., abiraterone, enzalutamide, Ra-223, sipuleucel-t). If applicable, patients should be weaned off steroids at least 1 week prior to starting treatment.

7. No prior chemotherapy for the treatment of mCRPC. Patients may have received docetaxel for the treatment of hormone-sensitive prostate cancer.

8. Prior treatment with non-chemotherapy investigational agents is permitted. There must be at least a 3-week washout period after stopping any investigational cancer agent.

9. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

    – Hemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN
- Patients must have creatinine clearance estimated using the Cockcroft-Gault equation or based on 24 hour urine test of ≥51 mL/min:

  $$\text{Estimated creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix 2).
11. Patients must have a life expectancy ≥ 16 weeks.
12. Male patients and their partners, who are sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination [see Appendix 3 for acceptable methods], throughout the period of taking study treatment and for 3 months after last dose of study drug(s) to prevent pregnancy in a partner.
13. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
14. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT, PET, MRI and/or bone scan and is suitable for repeated assessment.
15. Must have archival tissue available, be willing to undergo metastatic biopsy or have a sufficient plasma ctDNA concentration in order to perform next-generation DNA sequencing.
16. The study will require that 50% of enrolled subjects have homozygous deletions, deleterious mutations, or both in one or more of the DDR genes listed in Appendix 5. The other 50% of patients must have an intact DDR pathway (i.e., no mutations/deletions in genes listed in Appendix 5)[88].

3.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Previous enrollment in this study

3. Participation in another clinical study with an investigational product during the last 3 weeks

4. Any previous treatment with PARP inhibitor, including olaparib.

5. Other malignancy unless curatively treated with no evidence of disease for ≥5 years except: adequately treated non-melanoma skin cancer.

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

7. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment

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

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

10. Persistent toxicities (>Common Terminology Criteria for Adverse Event (CTCAE) grade 2) caused by previous cancer therapy, excluding alopecia.

11. Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

12. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

13. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

14. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but

are not limited to, uncontrolled ventricular arrhythmia, history of prior myocardial infarction, uncontrolled major seizure disorder, uncontrolled hypertension (BP ≥160/100), history of prior stroke, uncontrolled diabetes (hgb A1C >7), unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

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

16. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).

17. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

18. Patients with a known hypersensitivity to the testosterone cypionate or any of the excipients of the product

19. Patients with known active hepatitis (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids

20. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)

21. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no. 10)

22. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study.

23. Any psychological, familial, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.

24. Evidence of disease that, in the opinion of the investigator, would put the patient at risk from testosterone therapy (e.g. femoral metastases with concern over fracture risk, spinal metastases with concern over spinal cord compression, lymph node disease with concern for ureteral obstruction).

25. Patients with pain attributable to their prostate cancer

26. Tumor causing urinary outlet obstruction that requires catheterization for voiding. Patients that require catheterization to void secondary to benign strictures or other non-cancer causes will be permitted to enroll.

27. Prior history of deep venous thrombosis or pulmonary embolism within 5 years prior to enrollment in the study and not currently on systemic anticoagulation.

28. Patients with NYHA (New York Heart Association) class III or IV heart failure or history of a prior myocardial infarction (MI) prior to enrollment in the study.

4. STUDY PLAN AND PROCEDURES

4.1 Overall study design and flow chart

This will be a single arm, Phase II study designed to evaluate the clinical activity of bipolar androgen therapy (BAT) plus olaparib in patients with asymptomatic metastatic castration-resistant prostate cancer (mCRPC) (i.e. progressive prostate cancer in spite of serum testosterone <50 ng/dL) that has already progressed on abiraterone and/or enzalutamide (Figure 11). While DNA damage repair (DDR) deficiency is not required to be eligible for the study, all patients must have next-generation sequencing performed at baseline to assess DDR status. The study will require that 50% of enrolled subjects have homozygous deletions, deleterious mutations, or both in one or more of the DDR genes listed in Appendix 5. The other 50% of patients must have an intact DDR pathway (i.e. no mutations/deletions in genes listed in Appendix 5).

All patients will continue on androgen deprivation therapy (ADT) (i.e. surgical or medical castration), and should have a two-week washout from their most recent mCRPC therapy and weaned from steroids prior to enrollment. Eligible patients will initiate T enanthate or T cypionate 400 mg intramuscular every 28 days, which has been shown to result in rapid fluctuations between supraphysiologic and near castrate serum T levels in men maintained on ADT [11]. Patients will also receive olaparib 300 mg by mouth twice daily. One treatment cycle will be defined as 28-days, and consist of 1 dose of T enanthate or T cypionate on Day 1 combined with continuous daily dosing of olaparib (Days 1-28).

PSA will be measured on Day 1 of each treatment cycle prior to receiving T enanthate or T cypionate. Radiographic assessment with bone and CT scans will occur every 12-weeks. The primary endpoint will be PSA after 3-cycles of BAT plus olaparib (i.e. 12-weeks). Patients will be permitted to continue until disease progression by radiographic (per RECIST 1.1 or PCWG3) or clinical criteria (e.g. increasing pain), whichever comes first [95, 96]. Prior to completing 3-cycles of treatment, patients should not discontinue treatment for PSA progression alone; however, if after 3-cycles the PSA has not decreased 50% from baseline (i.e. PSA_{50} response) that patient may withdraw from the study if their treating physician feels it is in their best interest. It is also essential that PSA be measured before injection of Testosterone given that some patients may experience a transient increase in PSA immediately following T dosing. PSA values obtained at timepoints other than those required per protocol will be ignored and not used for the purpose of determining disease progression.

Blood and tumor tissue for secondary analyses and correlative studies will be collected. Metastatic biopsies will be obtained at baseline, on Day 8 of Cycle 1 and again upon progression when possible. This tissue will be used for molecular studies and to measure intratumoral androgen levels. Blood for molecular studies will be collected serially at

baseline, Day 8 of Cycle 1, Day 1 of Cycle 4 and at the time of progression (PSA, radiographic, or clinical).

The primary objective of this study is to determine the PSA_{50} response rate following 12-weeks of treatment with BAT plus olaparib, which will be defined as the proportion of men with a PSA at least 50% below baseline at this timepoint. Secondary objectives will be to determine the radiographic response rate (per RECIST 1.1), radiographic PFS (per RECIST 1.1), PSA PFS (per PCWG3), PFS (i.e. whichever occurs first: clinical, radiographic or PSA progression), overall survival, QoL changes, and to assess safety (per CTCAE v4.0) [95, 96].

Correlative work will be conducted in order to better understand the biology underlying response and resistance to BAT plus olaparib in men with mCRPC. Serial blood samples will be obtained from all patients, and metastatic tissue will be obtained at baseline and again at progression when possible. Examples of studies to be conducted may include, but are not limited to: evaluating for differences in response and disease progression in patients with/without mutations in genes involved in homologous recombination, studies to determine intratumoral androgen levels using LC/MS, assessing for evidence of dsDNA breaks, evaluating AR and AR-V expression at the protein and transcript levels, sequencing tumor DNA, and tumor transcript profiling studies.

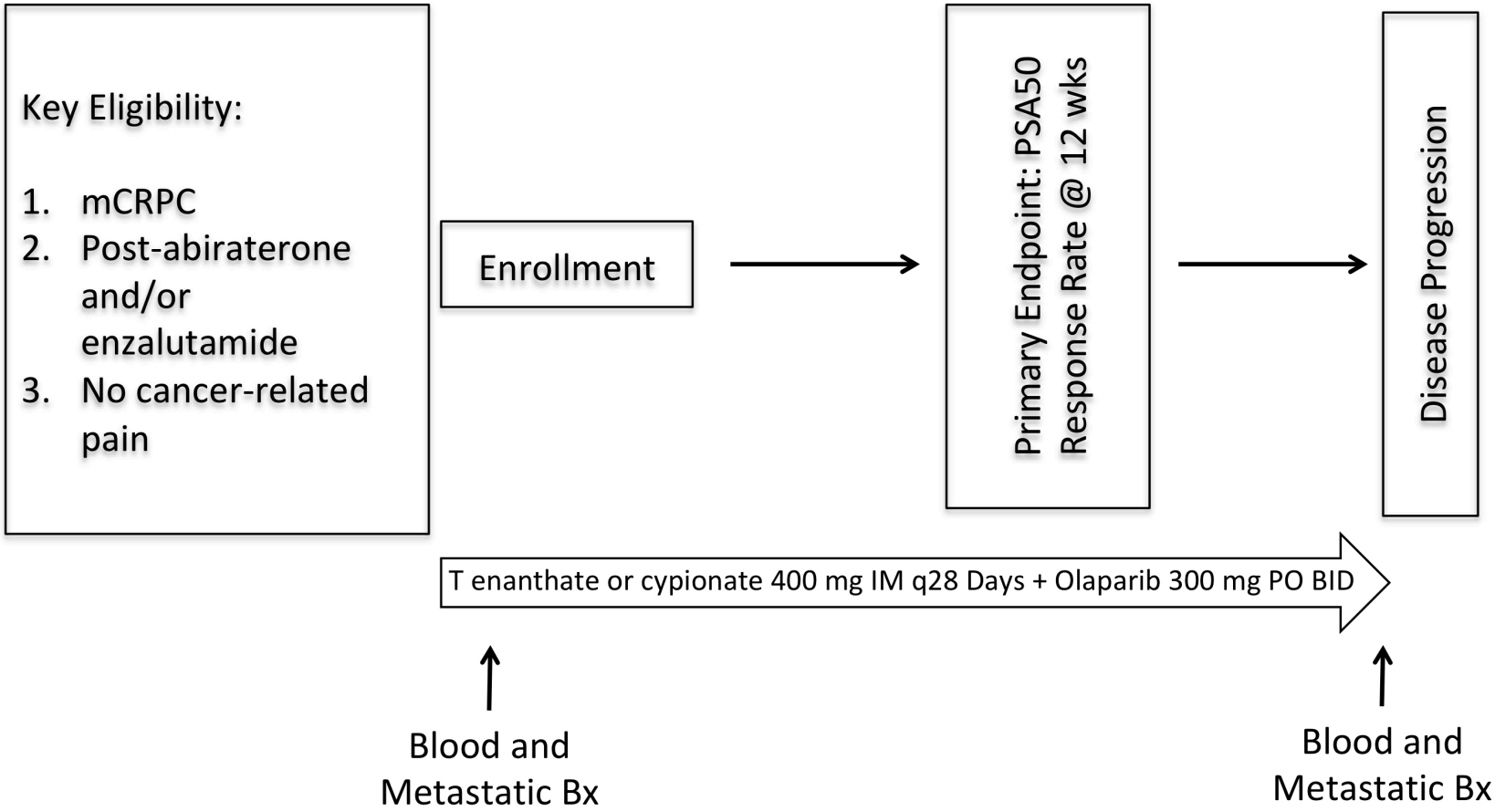

Figure 11. Study schematic. PSA50 = PSA decline ≥50% from baseline.

4.2 Discontinuation of investigational product

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

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event that, in the opinion of the Principal Investigator contraindicates further dosing
- Severe non-compliance with the study protocol that, in the opinion of the Principal Investigator or Sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits)
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Initiation of alternative anticancer therapy including another investigational agent
- Study drug held for >4 weeks due to an AE

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Biospecimens obtained as part of trial participation will be retained, however.

4.2.1 Procedures for discontinuation of a subject from investigational product

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 5.2.4, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone as an alternative.

4.3 Withdrawal from study

Subjects that withdraw prior to the 12-week timepoint will be replaced. Any subject needing to be replaced will be counted as a non-responder.

5. TREATMENT ASSESSMENTS AND EVALUATIONS

5.1 Recording of data

All data will be recorded in the electronic case report forms (eCRFs), which will be maintained on secure servers at the SCCA and/or UWMC. Patient data will be de-identified, and access to the de-identification key will only be available to the Principal Investigator and his designees as necessary.

5.2 Data collection at enrollment and follow-up

During the Treatment/Intervention Period study procedures and assessments must be done within 7 days (+/-) of the specified study visit date unless otherwise noted. Screening procedures and assessments must be done within 30 days prior to enrollment unless otherwise noted. End of Study procedures and assessments must be within 30 days of stopping study drug(s).

Note: If a subject withdraws from the study prior to the 12-week timepoint, the "End of Study" procedures will be completed at the time of withdrawal.

5.2.1 Screening (within 30 days of Cycle 1, Day 1)

1. Informed consent
2. Comprehensive medical history and physical exam, including height and weight, medication reconciliation, blood pressure, heart rate and ECOG performance status assessment
3. CBC (Complete blood count) with differential and platelet count
4. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2)
5. PSA
6. Testosterone
7. Estradiol
8. aPTT (activated partial thromboplastin time), PT/INR (prothrombin time/international normalized ratio)

9. Radiologic tests (i.e., CT chest/abdomen/pelvis and bone scan)

10. ECG

11. Metastatic biopsy

Note: If a biopsy cannot be safely performed, archival tissue obtained within the last year may be used as long as patient had castration-resistant prostate cancer, as determined by the treating physician, at that time.

5.2.2 Treatment/Intervention Period

1. Comprehensive medical history and physical exam, including weight, medication reconciliation, blood pressure, heart rate and ECOG performance status assessment [Day 1 of every cycle]

2. Olaparib dispensation [Day 1 of every cycle]

3. Unused olaparib collection [Day 1 of every cycle beginning Cycle 2]

4. Treatment with testosterone enanthate or testosterone cypionate [Day 1 of every cycle]

5. CBC (Complete blood count) with differential and platelet count [Day 1 of every cycle]

6. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2) [Day 1 of every cycle]

7. PSA [Day 1 of every cycle]

8. Testosterone [Cycle 1, Day 8 (+/- 7 days) and Cycle 2, Day 1]

9. Estradiol [Cycle 1, Day 8 (+/- 7 days) and Cycle 2, Day 1]

10. Radiologic tests (i.e. CT chest/abdomen/pelvis and bone scan) [Every 3 cycles beginning Cycle 4, Day 1]

11. ECG [within 7 days prior to starting study treatment and as clinically indicated]
12. Blood for exploratory biomarkers [Cycle 1, Day 1 and Cycle 1, Day 8 (+/- 7 days; optional)]
13. Optional metastatic biopsy [Cycle 1, Day 8 (+/- 7 days)]
14. Quality of life questionnaires (FACT-P and IIEF) [Every 3 cycles]
15. Brief pain inventory [Every cycle]

5.2.3 End of study

End of Study is defined as the last visit where the decision is made to discontinue treatment. All required procedures must be completed within 30 days of receiving the last dose of study drug(s). Treatment/Intervention Period assessments may used for the End of Study timepoint if within the 30 day timeframe.

1. Comprehensive medical history and physical exam, including weight, medication reconciliation, blood pressure, heart rate and ECOG performance status assessment
2. Unused olaparib collection
3. CBC (Complete blood count) with differential and platelet count
4. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2)
5. PSA
6. Radiologic tests (i.e., CT chest/abdomen/pelvis and bone scan)
7. Blood for exploratory biomarkers
8. Optional metastatic biopsy
9. Quality of life questionnaires (FACT-P and IIEF)
10. Brief pain inventory

5.2.4 Follow Up

A 30-day safety follow-up will be required (+/-7 days). End of Study assessments may be used for the follow-up timepoint if these have occurred +/-7 days of the follow-up visit.

1. Comprehensive medical history and physical exam, including weight, medication reconciliation, blood pressure, heart rate and ECOG performance status assessment
2. CBC (Complete blood count) with differential and platelet count
3. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2)

5.2.5 Long-term Follow Up

The Long-term Follow Up assessment is to confirm if patient is still alive, and to document the date of death if deceased. This may be conducted in person or remotely (i.e., via phone, email or postal). Long-term Follow Up will occur every 6 months (+/- 30 days) up to 2 years following last dose of study drug(s) or sooner if the study is terminated.

Study calendar

	Screening	Treatment/Intervention Period						End of Study	Follow Up[b]	Long-term Follow up[c]
		Cycle 1[a]		Cycle 2	Cycle 3	Cycle 4	Cycle ≥5			
	Day -30 to 0	Day 1 (±7 d)	Day 8 (±7 d)	Day 1 (±7 d)	Day 1 (±7 d)	Day 1 (±7 d)	Day 1 (±7 d)	≤30 d from stopping treatment	30 d (±3 d) from last dose of study drug(s)	Every 6 months (±30 d)
Informed consent	X									
Treatment with testosterone enanthate/cypionate		X		X	X	X	Every Cycle			
Olaparib dispensation		X		X	X	X	Every Cycle			
Unused olaparib collection				X	X	X	Every Cycle	X		
Demographics	X									
Medical history	X	X		X	X	X	Every Cycle	X	X	
Physical assessment	X	X		X	X	X	Every Cycle	X	X	
Vital signs	X	X		X	X	X	Every Cycle	X	X	
Height	X									
Weight	X	X		X	X	X	Every Cycle	X	X	
Performance status	X	X		X	X	X	Every Cycle	X	X	
ECG[d]	X									
Radiologic tests[e]	X					X	Every 3 Cycles[h]	X		
CBC with diff	X	X		X	X	X	Every Cycle	X	X	
CMP	X	X		X	X	X	Every Cycle	X	X	
PSA	X	X		X	X	X	Every Cycle	X		
Serum Testosterone	X		X	X						

Estradiol	X		X	X						
aPTT, PT/INR	X									
Urinalysis	X									
Metastatic biopsy	X[i]		X[j]					X[j]		
Blood for Exploratory biomarkers[f]		X	X[j]					X		
Quality of Life Surverys[g]		X				X	Every 3 Cycles[h]	X		
Brief Pain Inventory		X		X	X	X	Every Cycle			
Longterm survival follow up										X
Adverse events		X ----------X								

Abbreviations: CBC, Complete blood count with platelets and differential; CMP, complete metabolic panel (Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2); ECG, electrocardiogram; PSA, prostate-specific antigen; aPTT, activated partial thromboplastin time; PT, prothombin time; INR, international normalized ratio.

a. If a study assessment/test was done during the screening period, it does not need to be repeated if within 7 days of Cycle 1, Day 1.

b. End of Study visit may replace Follow Up visit if it occurs at 30 days

c. Long-term follow up to confirm if patient is still alive, and to document the date of death if deceased. This may be conducted in person or remotely (e.g. via phone, email or postal). Long-term follow up will occur up to 2 years following last dose of study drug(s)

d. ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

e. CT chest/abodmen/pelvis and bone scan.

f. Refer to section 6.3 of the protocol for details

g. FACT-P and IIEF surveys

h. Beginning Cycle 7, Day 1

i. Fresh metastatic tissue is preferred. However, if a biopsy cannot be safely performed, archival tissue obtained within the last year may be used as long as patient had CRPC at the time. For patients with PSA ≥20 ng/ml, plasma derived ctDNA may be used.

j. Biopsy and exploratory blood draw at this time point will be optional.

6. STUDY ASSESSMENTS

6.1 Efficacy

Efficacy will be determined by assessing PSA and radiographic changes (e.g. bone scan, CT scan) while on study. Ideally, these assessments will be performed at SCCA/UWMC, however, if necessary due to extenuating circumstances (e.g. insurance coverage issues) these may be performed at an outside lab/imaging center.

6.2 Safety

The Principal Investigator (Michael Schweizer, MD) is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.2.1 Definition of adverse events

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

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

6.2.2 Olaparib adverse events of special interest

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

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

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

6.2.3 Assessment of severity

Assessment of severity is one of the responsibilities of the sub-investigators and Principal Investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI

CTCAE v4.03. The determination of severity for all other events not listed in the CTCAE should be made by the treating physician (i.e. Sub-Investigator, Principal Investigator) based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (i.e., eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

6.2.4 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfills one or more of the following criteria:

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

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

Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

6.2.5 Assessment of relationship

All AEs will be evaluated for relationship to the medical treatment or procedure. The treating physician (i.e., Sub-Investigator, Principal Investigator) should document his/her opinion of the relationship of the event to study medication as follows:

- *Unrelated*- The adverse event is clearly not related to the investigational agent(s).
- *Unlikely*- The adverse event is doubtfully related to the investigational agent(s).
- *Possible*-The adverse event may be related to the investigational agent(s).
- *Probable*-The adverse event is most likely related to the investigational agent(s).
- *Definite*- The adverse event is clearly related to the investigational agent(s).

6.2.6 Early stopping due to adverse events

This study will stop early if >3 subjects experience a SAE determined to be at least possibly related to the study drugs, with the following exceptions:

- Hospitalization lasting ≤48 hours
- Non-life threatening hematologic toxicities (e.g. febrile neutropenia without evidence of septic shock, anemia)

6.2.7 Recording of adverse events

Adverse events will be recorded on electronic case report forms (eCRFs) using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the treating physician (i.e., Sub-Investigator, Principal Investigator) for severity, relationship to the investigational product, and possible etiologies. Adverse event assessments will then be verified by the Principal Investigator who will also determine whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTCAE grade attained
- Whether the AE is serious or not
- Causality rating against olaparib (yes or no)
- Action taken with regard to olaparib
- Causality rating against testosterone (yes or no)
- Action taken with regard to testosterone
- Outcome

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

- Date AE met criteria for serious AE
- Date treating physician (i.e. Sub-Investigator, Principal Investigator) became aware of serious AE
- Reason AE is considered serious
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

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

Time period for collection of adverse events

Adverse events and serious adverse events will be recorded from time of first dose of study drug(s), throughout the treatment period and including the follow-up period (30 days after the last dose of olaparib or testosterone, whichever occurred most recently).

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The treating physician (i.e. Sub-Investigator, Principal Investigator) is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

6.2.7.1 Adverse events after the 30 day follow up period

For Pharmacovigilance purposes and characterization, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE [e.g., non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e., after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the treating physician (i.e. Sub-Investigator, Principal Investigator) for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2.4. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Note: Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix 1 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Disease progression

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

New cancers

The development of a new primary cancer (including skin cancer) should be regarded as an AE (see Section 6.2.2). 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 patient's clinical condition, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

Deaths

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

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.2.7 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.

6.2.8 Reporting of serious adverse events

Investigators and other site personnel must report to AstraZeneca, any serious or unexpected adverse events that occur. A copy of the report for any serious or unexpected adverse events must be faxed to AstraZeneca. It is the responsibility of the investigator to compile all necessary information and ensure that these reports are submitted to AstraZeneca.

* A ***cover page*** should accompany the report indicating the following:

- External Scientific Research (ESR)

- D-Code Assigned by AstraZeneca
- The investigator's name and address
- The Protocol Title and AstraZeneca ESR reference number
- Causality of event(s)

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

**** Send SAE re ort and accom an in cover a e b wa o Email to*** [redacted]

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

Serious adverse events that do not require expedited reporting, still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

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

6.2.9 Laboratory safety assessment

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials. Coagulation [activated partial thromboblastin time (APTT) and international normalized ratio

[17]] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin.

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

Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 8.2.7.

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

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

In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix 1 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions

For blood volume see Section 7.1.

6.2.10 Physical examination

Physical examinations will occur as outline in Sections 5.2 and 5.3. Organ systems to be assessed will be based on the treating clinician's medical judgment.

6.2.11 ECG

ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

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

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

6.2.12 Vital signs

6.2.12.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured using an automated blood pressure cuff/heart monitor. For timings of assessments refer to Sections 5.2 and 5.3.

6.2.12.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer. For timings of assessments refer to Sections 5.2 and 5.3.

6.2.13 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 as defined in Section 8.2.7. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the investigator to AstraZeneca Patient Safety for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

6.3 Exploratory biomarkers

This study will incorporate a number of exploratory biomarkers. Given our rapidly evolving understanding of prostate cancer pathobiology and genetics, it is impossible to prospectively define all the relevant biomarkers for the patient population enrolled on this study. All samples will be collected at the timepoints indicated in Sections 5.2 and 5.3 of the protocol. Details regarding the collection, processing, shipping and storage of samples for exploratory research will be described in the Laboratory Manual. Examples of the studies to be conducted may include, but will not be limited to those described below. Additional studies aimed at understanding response and resistance to the study drugs may be added as new information becomes available.

6.3.1 DNA Damage Repair Gene Status

All patients will undergo targeted next-generation sequencing in order to evaluate for the presence of a DDR gene alteration at baseline. This will be accomplished using the UW-OncoPlex platform, which has been validated for use with tumor tissue derived DNA and cell-free tumor DNA (ctDNA)[97]. The preferred sample for sequencing is one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current DDR status of the tumor and are considered clinically most relevant. A fresh metastatic biopsy is therefore preferred for UW-OncoPlex testing. If patient refuses metastatic biopsy or it is felt that this cannot be conducted safely, the most recent tissue sample may be used, or if a patient has a PSA ≥20 ng/mL, a plasma sample may be used for ctDNA

sequencing. Optional biopsies will be requested at timepoints indicated in Sections 5.2 and 5.3.

Note: If prior to enrolling, a patient has already had their tumor sequenced using a clinical grade next-generation sequencing assays (e.g. FoundationOne, Caris, etc), these results may be used for determining baseline DDR gene mutational status. Tumor tissue should still be obtained as outlined above to confirm DDR status using UW-OncoPlex, however.

6.3.2 Protein expression studies

Protein expression studies will be conducted on circulating tumor cells (CTCs) and/or tumor tissue using immunofluorescence (IF) and immunohistochemistry (IHC), respectively. Expression of full-length AR (AR-FL), AR splice variants (AR-Vs), γ-H2AX as well as potentially other proteins will be assessed. IHC will be will be performed using commercially available antibodies and standard lab techniques. CTCs for protein studies will be isolated using the RareCyte platform, which involves density-based enrichment followed IF staining and digital microscopy[98].

6.3.3 Transcript profiling studies

Transcript profiling studies will be conducted on circulating tumor cells (CTCs) and/or tumor tissue. Transcript profiling on tumor tissue will be performed using RNA-seq, qRT-PCR or other gene expression profiling methods as appropriate (e.g. NanoString), and will follow standard lab techniques. AdnaTest will be used to isolate CTCs for transcript expression studies[45]. AdnaTest isolates CTCs using antibody coated magnetic beads, which are designed to select populations of prostate cancer cells, and is suitable for transcript profiling studies. Blood samples will be processed using AdnaTest and used for multiplexed qRT-PCR studies.

6.3.4 Tissue and Serum Androgen Levels

Tissue and serum androgens (e.g. T and DHT) and hormonal substrates (e.g. DHEA-S) will be determined in serum and metastatic biopsy specimens using liquid chromatography-mass spectrometry (LC/MS) according to previously described methods[99-102].

6.4 Patient reported outcomes (PRO)

The FACT-P and IIEF quality of life questionnaires will be administered periodically throughout the duration of the study (Appendix 4). Patients will be provided with blank questionnaires and encouraged to complete these at home prior to scheduled clinic visits as outlined in Sections 5.2 and 5.3. These may also be completed in the clinic if preferred by the patient. If completed at home, questionnaires must be completed within the time windows indicated in Sections 5.2 and 5.3. Scoring of these surveys will be performed as previously described [103, 104].

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

Table 2 provides an approximation of the amount of blood that will be drawn for the safety and biomarker assessments outlined in Sections 5.2 and 5.3. In general, these labs will not all be drawn at the same visit, and this table provides an estimate for the upper limit of blood volume required from a patient at any given visit. The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on the study treatment becomes available.

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

Table 2. Volume of Blood to Be Drawn From Each Subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety[1]	Clinical chemistry	5	1	5
	Hematology	3	1	3
	Coagulation	3	1	3
	Hepatitis panel	5	1	5
Exploratory biomarker research	CTC studies	10	2	20
	ctDNA studies	10	1	10
	Serum hormone levels	10	1	10
Total		46	8	56

1. The sample volumes for safety assessments are approximate volumes that are subject to change. Additional blood samples may be needed depending on the results of these studies and if patients require follow up testing or undergo additional procedures (e.g. fresh metastatic biopsy).

7.2 Handling, storage and destruction of biological samples

Biospecimen samples will be stored for up to five years following the completion of this study. Samples will be stored at University of Washington and/or Fred Hutchinson Cancer Research Center (UW/FHCRC). These samples may also be sent to our research partners participating in this study, including AstraZeneca. Specimens will not be used for reasons unrelated to this research study. All specimens will be kept in locked research laboratories at UW/FHCRC. The use of these specimens will be supervised by the Principal Investigator (Michael Schweizer, MD) and his designees.

8. STUDY CONDUCT

8.1 Restrictions during the study

8.1.1 Grapefruit juice

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

8.1.2 Contraception

Patients with partners of child bearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception. This should be started from the signing of the informed consent and continue throughout period of taking study medication and for 3 months after last dose of study drug. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

For details refer to Appendix 3 Acceptable Birth Control Methods.

8.2 Treatments

8.2.1 Identity of investigational product(s)

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

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

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

8.2.2 Olaparib doses and treatment regimens

Olaparib will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib will be dispensed to patients on Day 1 and every 28 days thereafter until the patient completes the study, withdraws from the study or closure of the study.

Study treatment is available as tablets containing 50mg of olaparib.

Patients will be administered olaparib twice daily at 300 mgs bid continually. 300 mg olaparib 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.

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

Dose Reductions

For guidance on dose reductions for management of AEs refer to Section 8.2.6.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 8.3.

Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BD.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

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

8.2.3 Testosterone

Testosterone esters are less polar than free testosterone. Testosterone esters in oil injected intramuscularly are absorbed slowly from the lipid phase; thus, testosterone enanthate or testosterone cypionate can be given at intervals of two to four weeks. These two forms of testosterone exhibit identical pharmacokinetic properties and may be used interchangeably in this study based on availability at the pharmacy [54]. These agents are administered as intramuscular injections given deep in the gluteal muscle. They should not be given intravenously. Testosterone cypionate is in cottonseed oil with benzyl alcohol as a preservative. Testosterone enanthate is in sesame oil with chlorobutanol as a preservative.

Testosterone in plasma is 98 percent bound to a specific testosterone-estradiol binding globulin, and about 2 percent is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its half-life.

About 90 percent of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6 percent of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways. The half-life of testosterone enanthate is approximately 4.5 to 8 days, and has been shown to consistently result in supraphysiologic serum T levels following an intramuscular dose of ≥250 mg (Figure 12) [54].

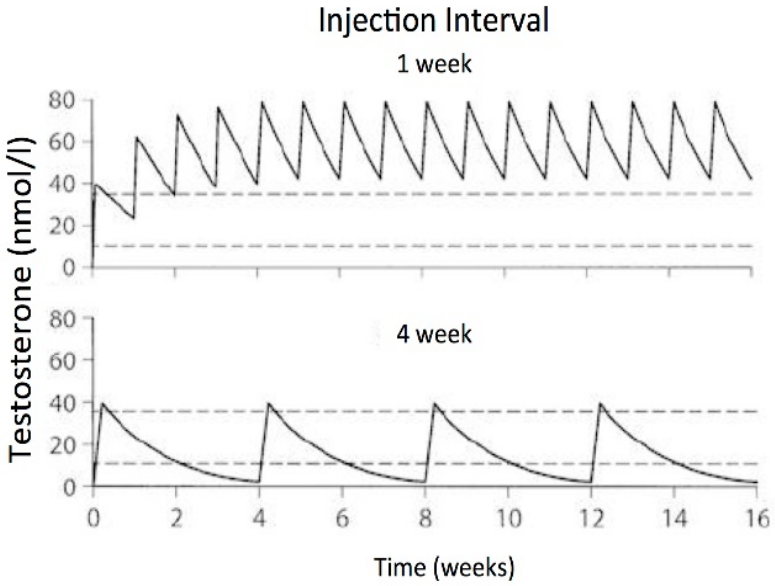

Figure 12: Modeled T Kinetics with different T enanthate dosing schedules (250 mg IM). Dashed line indicates physiologic T range (adapted from Nieschlag, *et al*[54]).

Testosterone Precautions

1. Patients with benign prostatic hypertrophy may develop acute urethral obstruction. Priapism or excessive sexual stimulation may develop.
2. Oligospermia may occur after prolonged administration or excessive dosage.
3. Testosterone Cypionate and Testosterone Enanthate should not be used interchangeably with testosterone propionate because of differences in duration of action.
4. Testosterone Cypionate and Testosterone Enanthate are not for intravenous use.

Drug interactions

1. Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.
2. Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
3. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Drug/Laboratory test interferences
Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Adverse Reactions
The following adverse reactions in the male have occurred with some androgens:

1. Endocrine and urogenital: Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages.
2. Skin and appendages: Hirsutism, male pattern of baldness, seborrhea, and acne.
3. Fluid and electrolyte disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.
4. Gastrointestinal: Nausea, cholestatic jaundice, alterations in liver function tests, rarely hepatocellular neoplasms and peliosis hepatis.
5. Hematologic: Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.
6. Nervous system: Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.
7. Allergic: Hypersensitivity, including skin manifestations and anaphylactoid reactions.
8. Miscellaneous: Inflammation and pain at the site of intramuscular injection.

Drug Abuse and Dependence
Controlled Substance Class:
Testosterone is a controlled substance under the Anabolic Steroids Control Act, and testosterone have been assigned to Schedule III.

Overdosage
There have been no reports of acute overdosage with the androgens.

Administration

Testosterone injections are for intramuscular use only. It should not be given intravenously. Intramuscular injections should be given deep in the gluteal muscle.

Supply

Testosterone is commercially available. It will be purchased for the study through the SCCA/UWMC pharmacy and billed to the trial.

Testosterone Enanthate Injection, USP, 200 mg/mL is available as:
5 mL Multiple Dose vial, Cartons of 1 vial NDC 0143-9750-01

Testosterone Cypionate Injection, USP, 200 mg/mL is available as:
10 mL Multiple Dose vial, Cartons of 1 vial NDC 0574-0820-10

8.2.4 Olaparib Labelling

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

Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrollment 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 the olaparib tablets should be taken at approximately the same time each morning and evening

8.2.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. For olaparib, the investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage. Testosterone vials should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP]. Protect from light. Use carton to protect contents from light until used.

8.2.6 Management of toxicity of *olaparib*

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

When dose reduction is necessary patients will take one 150 mg tablet and one 100 mg tablet twice daily or two x 100 mg tablet twice daily.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors).

8.2.7 Management of hematological toxicity

8.2.7.1 Management of anemia

Table 3 Management of anemia

Hemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl. Subsequent occurrences: If Hb< 10 *but* ≥ 9 g/dl investigator judgement to continue olaparib with supportive treatment (eg transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step). If Hb< 9 *but* ≥ 8 g/dl, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to 250 mg twice daily as a first step and to 200 mg twice daily as a second step).
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 8.2.7.3 for the management of this.

8.2.7.2 Management of neutropenia, leukopenia and thrombocytopenia

Table 4 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 8.2.7.3.

8.2.7.3 Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard

hematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

8.2.8 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

8.2.8.1 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.

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.

8.2.8.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (eg, 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered (eg, dopamine receptor antagonist, antihistamines or dexamethasone).

8.2.8.3 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 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the primary investigator (Dr. Michael Schweizer).

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

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

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

Table 5 **Dose reductions for olaparib treatment.**

NOTE: Dose of testosterone will remained fixed throughout the study. Dose reductions in testosterone could result in physiologic serum T levels, which in contrast to supraphysiologic levels, may promote tumor growth.

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300mg twice daily	250mg twice daily	200mg twice daily

8.3 Concomitant and post-study treatment(s)

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

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 with olaparib.

If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150mg bd for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Strong or Moderate CYP3A inducers

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

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

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

P-gp inhibitors

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

Effect of olaparib on other drugs

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

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6.

The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

Anticoagulant Therapy

Patients who are taking warfarin are not permitted to enroll in the study. Subcutaneous heparin and low molecular weight heparin are permitted. Patients that can be safely transitioned to heparin will be permitted to enroll.

Anti-emetics/Anti-diarrheals

If a patient develops nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs (see section 6.2) 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 baseline, provided the 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 patient 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

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

denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

Subsequent therapies for cancer

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

8.3.1 Medications that may NOT be administered

No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted while the patient is receiving study medication.

8.4 Treatment compliance

Patients will utilize a Pill Diary throughout the duration of the study to ensure compliance with treatment.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 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 Subject data protection.

9.2 Ethics and regulatory review

The local IRB must review and approval the protocol and informed consent prior to study activation. The IRB must comply with applicable local and national laws and regulations, including protections against conflicts of interest. Prior to site activation, the following regulatory items must be completed:

- Protocol is signed and understood by Principal Investigator
- Investigator's Brochure or product labeling, if applicable, is reviewed and understood by Principal Investigator and maintained in a file
- Protocol, protocol amendments, and informed consent forms are approved by IRB and documentation of IRB name and address and approval are maintained on file with the Principal Investigator

9.3 Informed consent

Written informed consent will be obtained by the study Investigator or a study sub-Investigator working on this study. An explanation of the nature of study, its purpose, procedures involved, expected duration, potential risks and benefits will be provided to each participant by the treating physician (i.e., Sub-Investigator, Principal Investigator) or the

research nurse. Each participant will be informed that participation in the study is voluntary and that he may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment. Participants will be allowed time needed to make an informed decision. Participants will be encouraged to ask questions about the study and the consent before signing the consent form. Original signed consent forms will be filed in each patient's research chart, while each patient will receive a copy of the consent document. No patient will enter the study before his informed consent has been obtained.

The Research Coordinator and Principal Investigator (Michael Schweizer, MD) will be responsible for reviewing the consent forms and verifying eligibility. Once it has been confirmed that a new candidate has provided consent and is eligible to participate in the study, the patient will be registered and assigned a unique study identification number.

9.4 Changes to the protocol and informed consent form

Any changes to the protocol or consent will be made in the form of an amendment and must be approved by the IRB before implementation. These changes may only be made by the Principal Investigator (i.e., Michael Schweizer, MD).

10. STUDY MANAGEMENT

10.1 Training of study site personnel

Prior to opening this study for accrual, each participating site will be required to have a Site Initiation Visit (SIV). The SIV will involve a presentation by the Principal Investigator to review the protocol in detail. The SIV should be attended (in person or virtually) by the Principal Investigator, study coordinator, investigational drug services representative and any other sub-investigators. If any of the aforementioned personnel are unable to attend the SIV, the participating site will be responsible for distributing the protocol and SIV presentation for review. Training should be documented on delegation logs at each participating site.

10.2 Monitoring of the study

Trial monitoring will be in accordance with the Fred Hutchinson Cancer Research Center (FHCRC)/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the

applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Additionally, scheduled meetings will take place weekly and will include the Principal Investigator (Michael Schweizer, MD), research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.

During these meetings the Sub-Investigators/ Principal Investigator will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

10.2.1 Source data

Source data will be maintained in study binders or electronically in secure servers as appropriate. Servers will be maintained at SCCA/UWMC and any hard copies of source data will be kept in a locked office or locked filling cabinets.

11. EVALUATION AND CALCULATION OF VARIABLES

Prostate cancer has a tendency to metastasize to bone and lymph nodes and is often associated with non-measurable metastatic disease per RECIST 1.1 criteria, even in its later stages [96, 105]. To maximize patient eligibility, those with non-measurable disease at baseline (per RECIST 1.1) will be permitted to enroll. Because evaluating for objective radiographic response will not be possible in all patients enrolled, we will determine the effects of treatment on PSA. The primary objective of this study will therefore be to determine the proportion of patients with ≥50% decline in PSA from baseline following initiation of treatment (i.e. PSA_{50} response rate). As recommended by the PCWG3, this will be assessed following 12-weeks of BAT plus olaparib therapy [95].

11.1 Calculation or derivation of efficacy variable(s)

PSA Response: The percent decline in PSA compared to baseline (i.e. most recent PSA value prior to first dose of study drugs) will be calculated for each patient for every on-study PSA value obtained. PSA_{50} response will be defined as a decline in PSA ≥50% compared to baseline. The primary objective is to determine the PSA_{50} response rate (i.e. proportion of patients achieving a PSA_{50} response) 12-weeks after initiating therapy.

PSA Progression: PSA progression will be defined as follows:

- For subjects showing an initial decline in PSA from baseline, PSA progression will be defined as an increase in PSA that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend).

- For those subjects with no decline in PSA from baseline, PSA progression will be defined as an increase in PSA that is ≥25% and ≥2 ng/mL after 12 weeks.

Radiographic Response: RECIST 1.1 guidelines will be used to define measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) [96]. Measurable vs. non-measurable lesions will be defined as follows:

- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and those that can truly not be measured (i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques).

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should within the 28-day screening period.

CT chest/abdomen/pelvis should be used to characterize each identified and reported lesion at baseline and during follow-up. Ideally iodinated contrast should be used, but if this is not possible (e.g. contrast allergy, renal insufficiency), then all subsequent scans should also forgo the use of contrast.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is required.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as ***target lesions*** and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Radiographic response will be defined as a complete response (CR) or partial response (PR). The following response criteria, modified from RECSIT 1.1, will be used:

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum LD of target lesions (including new measurable lesions), compared to the nadir sum LD
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the nadir sum LD since the treatment started

Survival Endpoints:

- Progression free survival (PFS) will be defined as the time from the start of treatment until disease progression (per modified RECIST criteria or PCWG3 criteria for bone lesions), clinical progression (as determined by the treating physician), or death, whichever occurs first.
- PSA PFS will be defined as the time from the start of treatment until PSA progression (as defined by PCWG3 criteria) [95].
- Overall survival (OS) will be defined as the time from the start of treatment until death from any cause.

It is important to note that bone metastases are considered non-measurable lesions. Determining progression in bone metastases will therefore be defined according to PCWG3 criteria as follows:

- Appearance of at least two new lesions on bone scan, with at least two additional lesions on confirmatory bone scan. Confirmatory bone scan should ideally occur at the next planned scan according to the Schedule of Study Assessments, but no earlier than 4 weeks.
- If at least two additional new lesions are seen on the confirmatory scan, the date of progression is the date of the bone scan when the first two new lesions were documented

- Changes in intensity of uptake alone do not constitute either progression or regression

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

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

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

There are currently no identified OAEs for olaparib

11.3 Calculation or derivation of patient reported outcome variables

Quality of life (QOL) will be recorded through the FACT-P and the International Index of Erectile Function (IIEF) surveys. These instruments has been previously validated and are used extensively in clinical trials to assess the effects of treatment intervention on quality of life. Details regarding these surveys can be found in Appendix 4.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

The safety and efficacy analysis sets will include all subjects that received at least one dose of the study drug. Subjects that drop out, for any reason, prior to 12-weeks (i.e. primary endpoint assessment timepoint) will be replaced.

12.2 Methods of statistical analyses

12.2.1 Safety Analyses

We will characterize AEs by type and grade as outlined in Section 6.2. Safety will be summarized as the severity and frequency of a given AE.

12.2.2 Efficacy Analyses

Primary Objective

The primary objective will be to determine the PSA_{50} response rate (i.e. proportion of patients with a decline in PSA ≥50% from baseline) to BAT plus olaparib in mCRPC patients following 12-weeks of therapy. This will be calculated as the percentage with 95% confidence interval (CI) of the total number of subjects that achieved a PSA_{50} response. Subjects who drop out of the study prior to 12-weeks will be counted as treatment failures (i.e. non-responders), however, these patients will be replaced.

Secondary Objectives

Secondary objectives will include determining: overall survival, radiographic PFS, PSA PFS, PSA_{50} response rate (i.e. decline in PSA ≥50% from baseline), and radiographic response rate. Definition for progression and response endpoints are provided in Section 11.1. Survival endpoints will be presented with Kaplan-Meier curves, and the median survival with 95% CI will be calculated. Rates will be reported as percentages with 95% CI. Best on study PSA and radiographic response for each patient will be presented in a waterfall plot. Average change in QOL scores (total and for each domain) for each survey will be calculated at each timepoint. A paired t-test will used to assess for statistically significant changes in QOL from baseline to the 12-week timepoint, and linear mixed effects models will be used to evaluate trends over all timepoints.

12.2.3 Exploratory Analyses

Exploratory correlative work will be conducted with the goal to understand the mechanism mediating response and resistance to BAT plus olaparib, and to determine if there are biomarkers that are predictive of response to combination therapy. Examples of studies to be conducted may include, but are not limited to: evaluating for differences in response and disease progression in patients with/without mutations in genes involved in homologous recombination, studies to determine intratumoral androgen levels using LC/MS, assessing for evidence of dsDNA breaks, evaluating AR and AR-V expression at the protein and transcript levels, sequencing tumor DNA, and tumor transcript profiling studies. Baseline exploratory biomarker levels/values, as well as changes in these levels/values pre-/post-treatment will be correlated with the primary endpoint and secondary endpoints using chi-square tests and logistic regression, or (for PFS and OS) using proportional hazards models, Kaplan-Meier methods and log-rank tests.

12.3 Determination of sample size

The primary objective will be to determine the PSA_{50} response rate for combination BAT and olaparib 12-weeks after starting therapy. PSA_{50} response rate will be defined as the proportion of patients achieving a ≥50% decline in PSA from baseline. Across two prior studies testing BAT in men with CRPC, we observed a PSA_{50} response rate of ~30% [11, 56]. In a prior study testing olaparib in men with CRPC, approximately 75% of patients with evidence of

DNA damage repair deficiency (DDR) had a PSA_{50} response to olaparib monotherapy[88]. Therefore, given that we will require 1/2 of the study cohort to have evidence of DDR deficiency and the other half to have intact DDR genes, we estimate that the null rate (H0) for combination therapy will be approximately 50%. Combination therapy will be deemed worthy of further study if we detect a PSA_{50} response rate of ≥75% (H1) for the entire study cohort, which would compare favorably to a null (H0) PSA_{50} response rate of 50%. Based on these assumptions, a sample size of 30 patients will provide 82% power to detect a difference between the null (H0) and alternative (H1) hypotheses at a two-sided type I error (α) of 0.05.

A key secondary objective of this study is to evaluate candidate biomarkers for their ability to discriminate between responders and non-responders to BAT plus olaparib. Because DNA damage repair (DDR) deficiency appears to predict for responses to olaparib and may predict for response to BAT, we will ensure that half of the patients enrolled (N=15) will have DDR deficiency. DDR deficiency will be defined by the presence of homozygous deletions, deleterious mutations, or both in DNA-repair genes (e.g. *BRCA 1/2*, *ATM*) previously shown to associate with response to olaparib [88]. Assuming a two-sided type I error (α) of 10% and a PSA_{50} response rate of 13/15 for patients with DDR deficiency (based on prior experience), we will have 65% power to detect a difference in PSA_{50} response versus 8/15 patients without DDR deficiency [88]. Similarly, we will have 98% power to detect a difference versus 4/15 patients without DDR deficiency.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Overdose

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

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg bid (tablet).

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

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

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

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

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.2.7. For other overdoses, reporting should be done within 30 days.

13.1.1 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

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

The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

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Appendix 1: 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.

During the course of the study the treating physician (i.e. Sub-Investigator, lead/ Principal Investigator) will remain vigilant for increases in liver biochemistry. The Principal Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Principal Investigator participates, together with AstraZeneca clinical project representatives, 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 Investigational Medicinal Product (IMP).

The Principal 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 medication 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 IMP, can be found to explain the combination of increases, eg, 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 patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN

The Principal Investigator will without delay review each new laboratory report, and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see above) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Principal Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the treating physician (i.e. Sub-Investigator, Principal Investigator) will:

- Notify the Principal Investigator who will notify AstraZeneca representative.
- The treating physician (i.e. sub-investigator, Principal Investigator) contacts the Principal Investigator, to provide guidance, discuss, and agree on an approach for the study patient's follow-up and the continuous review of data. Subsequent to this contact the treating physician (i.e. sub-investigator, Principal Investigator) will:
  - Monitor the patient 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 Study Physician.
  - Complete the 3 Liver eCRF Modules as information becomes available.
- If at any time (in consultation with the treating phsyician) 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 3 weeks after the biochemistry abnormality was initially detected, the treating physician contacts the Principal Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. 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 Principal 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 AstraZeneca standard processes.
  - 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 3 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 assessment 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 patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

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

- Determine if there has been a significant change in the patients' 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 notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's Law Criteria met of this Appendix

[#] 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 Principal Investigator, this may be in consultation with the treating 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 should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- 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, or did the patient 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: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:

- Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met If there is no significant change no action is required

- If there is a significant change follow the process described in this Appendix

[#] 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 Principal Investigator; this may be in consultation with the treating physician if there is any uncertainty.

Reference

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix 2: ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Reference

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Appendix 3: Highly Effective Methods of Contraception

Olaparib is regarded as a compound with medium/high foetal risk.

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

Acceptable Non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 3 months after the last dose of study drug. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (eg., levonorgestrel releasing IUS -Mirena®) PLUS male condom

Intravaginal device (e.g., EE and etonogestrel) PLUS male condom

Appendix 4: Quality of Life Surveys: FACT-P and IIEF

References

Esper P, Mo F, Chodak G et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997; 50: 920-928.

Rosen RC, Riley A, Wagner G et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49: 822-830.

Appendix 5: DNA Damage Repair Pathway Genes of Interest

This study will require that 50% of enrolled subjects have homozygous deletions, deleterious mutations, or both in one or more of the DNA damage repair (DDR) genes (i.e. DDR deficiency). A list of genes previously shown to associate with response to olaparib is below. Given that our understanding of genomic factors that may predict response to olaparib is evolving, additional alterations in genes associated directly or indirectly in homologous recombination repair response or PARP inhibitor sensitivity may be used at the PI's discretion. The other 50% of patients must have an intact DDR pathway (i.e. no mutations/deletions in these genes).

DDR genes of interest:

- *BRCA2*
- *ATM*
- *FANCA*
- *CHEK2*
- *BRCA1*
- *PALB2*
- *HDAC2*
- *RAD51*
- *MLH3*
- *ERCC3*
- *MRE11*
- *NBN*
- *CDK12*

Reference

Mateo J, Carreira S, Sandhu S et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 2015; 373: 1697-1708.