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

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.

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]

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.

- 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

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.

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.

- 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.

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.

- 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.

- 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)

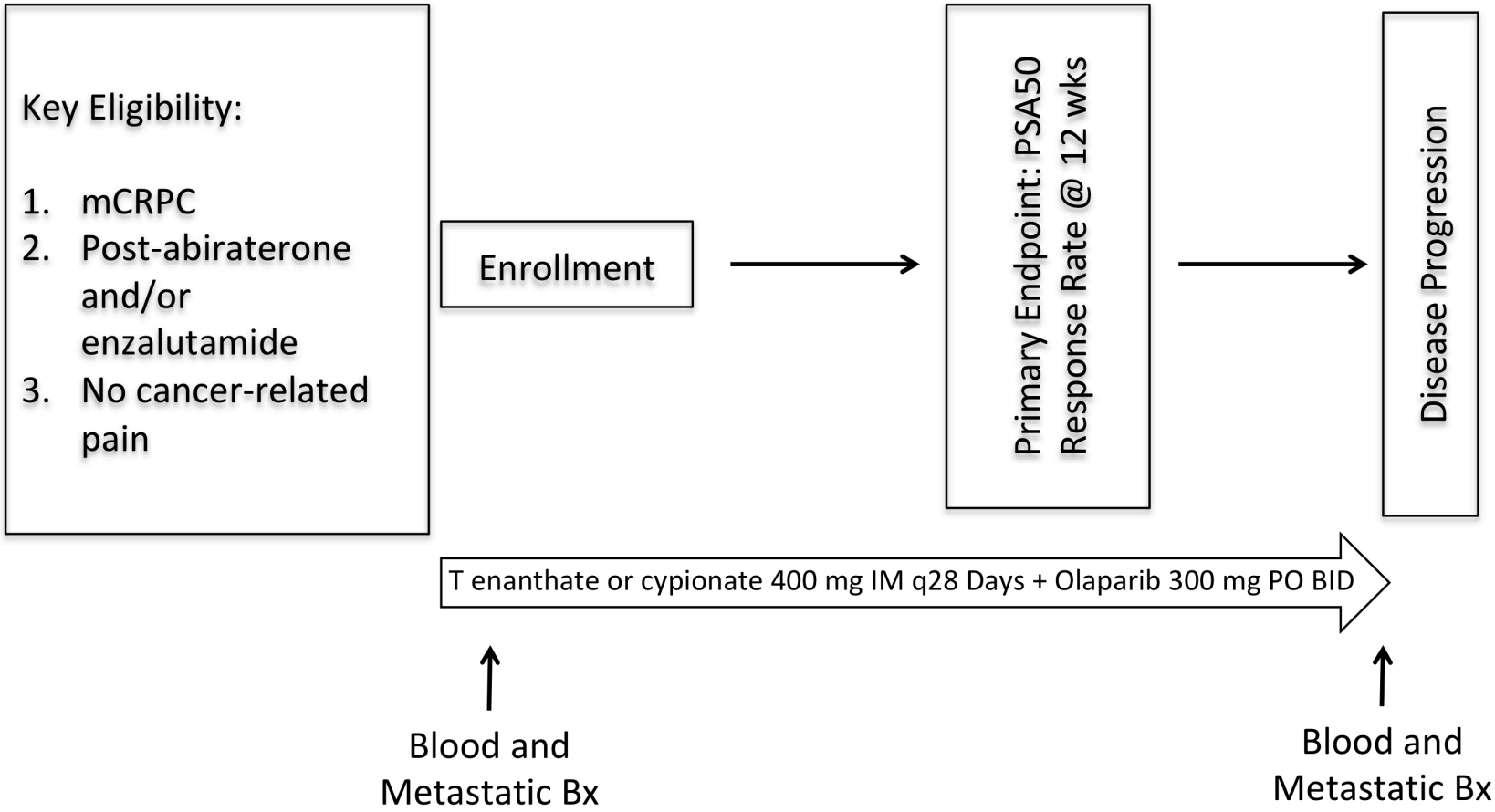

Figure 11. Study schematic. PSA50 = PSA decline ≥50% from baseline.

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

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)

[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.

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.

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

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

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.

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