Clinical Study Protocol	
Drug Substance	Olaparib
Study Code	ESR-18-13807
Version	6
Date	August 16, 2021

A study of serum folate levels in patients with solid tumors treated with olaparib

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Sponsor:

Regulatory Agency Identifying Number(s):

VERSION HISTORY

Version 3, January 4, 2019
Version 4, June 16, 2020
Version 5, December 06, 2020
Version 6, August 16, 2021

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

1. Participants will be screened for eligibility with medical history, physical exam, prior treatment, history of anemia and blood tests including baseline CBC, reticulocyte count, ferritin, B-12 and serum folate level
2. If inclusion criteria are met and after signing a consent form, participants will start olaparib 300 mg twice daily, commercially approved
3. Assessment of CBC/serum folate will occur every 2 weeks for the first 3 months and then monthly for a total of 6 months from the time of enrollment onto study therapy. If the patient develops folate deficiency and requires folate replacement, CBC/serum folate and reticulocyte count will occur every 2 weeks for 12 months.
4. One-time measurement of serum folate to occur one month after completion or discontinuation of therapy with olaparib
5. If folate deficiency is identified (defined as any level below normal) at any time point, the following parameters will be assessed in 2 weeks or at the next visit/assessment point: a repeat CBC/serum folate level along with B-12, LDH, reticulocyte count, methylmalonic acid, and homocysteine. These labs (CBC/serum folate level, B-12, LDH, reticulocyte count, methylmalonic acid, and homocysteine) need to be drawn once- 2 weeks after initial folate deficiency is identified for confirmation purposes and to rule out co-existing B-12 deficiency or other causes of anemia.
6. Once folate deficiency is confirmed in the setting of hemoglobin (Hgb) less than 12 g/dl but above 10.0 g/dl, patients will be randomized to folate supplementation or placebo. At that point, assessment of CBC/reticulocyte count and folate levels will continue every 2 weeks.
7. If Hgb is above 12.0 g/dl and no folate deficiency is identified, patients will not be randomized. Assessment of CBC/serum folate will continue every 2 weeks for the first 3 months and then monthly for a total of 6 months from the time of enrollment onto the study.
8. If folate deficiency is identified in setting of Hgb less than 10.0 g/dl, patients will not be randomized but will receive folic acid supplementation at 1 mg daily. These patients will have weekly assessments of CBC/reticulocyte count and folate levels until Hgb improves to a level above 10.0 g/dl. At that point, assessment of CBC/reticulocyte count and folate levels will change back to every 2 weeks. However, folic acid replacement will continue as initiated.
9. If a patient is already on folic acid supplements and continues to experience folate deficiency with a Hgb less than 10.0 g/dl, then folic acid dose can be increased to 2 mg daily or higher, at the discretion of the investigator. These patients will have weekly assessments of CBC/reticulocyte count and folate levels until Hgb improves to greater than 10.0 g/dl. At that point, assessment of CBC/reticulocyte count and folate levels will change back to every 2 weeks. However, folic acid replacement will continue at the last dose.
10. If folate deficiency is identified again in a patient who is already on folic acid supplementation, the following parameters will be assessed in 2 weeks or at the next

visit/assessment point: a repeat CBC/serum folate level along with B-12, LDH, reticulocyte count, methylmalonic acid, and homocysteine (see item # 5).

11. Tumor assessment will be performed as per treating physicians decision and would include regular clinical exams, tumor marker monitoring, and imaging (body CT scans) at every 3 -6 month interval
12. Safety assessments will be performed at every clinic visit
13. Data on *BRCA* testing results (if performed as standard of care) will be collected at the time of enrollment and updated throughout the study duration.

1.1.1 Table of Schedule of Activities

1.1.1 A - PATIENTS WITH NORMAL FOLATE

	SCREENING	CYCLE /MONTH#1-3	CYCLE / MONTH #1-3 BIWEEKLY LABS	CYCLE / MONTH #4 +	END OF TREATMENT (1 MONTH POST STUDY TREATMENT
Physical exam	X	X	X	X	X
Medical history	X	X			
Prior treatment	X	X	X		
Prior history of anemia	X	X	X		
Con Meds	X	X	X	X	X
Adverse effects	X	X	X	X	X
CBC w/ diff	X	X	X	X	
CMP	X	X		X	
Pt/PTT/INR*	X[1]				
Urinalysis*	X [1]				
Urine pregnancy test	X[1]	X[1]			
Reticulocyte count	X				
Ferritin	X				
B-12	X				

Folate	X	X	X	X	X
LDH					
Methylmalonic Acid					
Homocysteine					

1. If clinically indicated

1.1.1 B - **PATIENTS WHO DEVELOP FOLATE DEFICIENCY**

	CYCLE/ MONTH X DAY X + FOLATE DEFICIENCY IDENTIFIED RETURN IN 2 WKS	CYCLE/ MONTH X DAY #1	CYCLE/ MONTH X (IF Hgb less than 10.0 g/dl) weekly	CYCLE/ MONTH X Biweekly labs (IF HGB is above 10.0 g/dl	END OF TREATMENT (1 MONTH POST STUDY TREATMENT)
Physical exam		X			X
Con Meds		X		X	X
Adverse effects		X		X	X
CBC w/Diff	X	X	X	X	
CMP		X			
Folate	X	X	X	X	X
Ferritin	X				
B-12	X				
Reticulocyte Count	X	X	X	X	
LDH	X				
Methylmelanic Acid	X				

Homocysteine	X				

1.2 Synopsis

Protocol Title: A study of serum folate levels in patients treated with olaparib

Rationale:

Olaparib as well as other PARP inhibitors are known to cause hematologic toxicity, most commonly, macrocytic anemia regardless of the cancer type treated. The development of anemia may lead to blood transfusions, dose reductions and delay as well as drug discontinuation[1]. The cause of anemia is poorly understood. We have observed folate deficiency (<7 ng/mL) in 66% of patients treated with olaparib in a small group of patients with advanced ovarian and metastatic breast cancer occurring within weeks of treatment initiation with olaparib[2, 3]. Folate deficiency is a known cause of macrocytic anemia. However, it has not been previously reported in association with olaparib therapy. In our cohort of patients, folic acid replacement allowed us to avoid or decrease the need for blood transfusions, olaparib dose reduction and discontinuation of therapy.

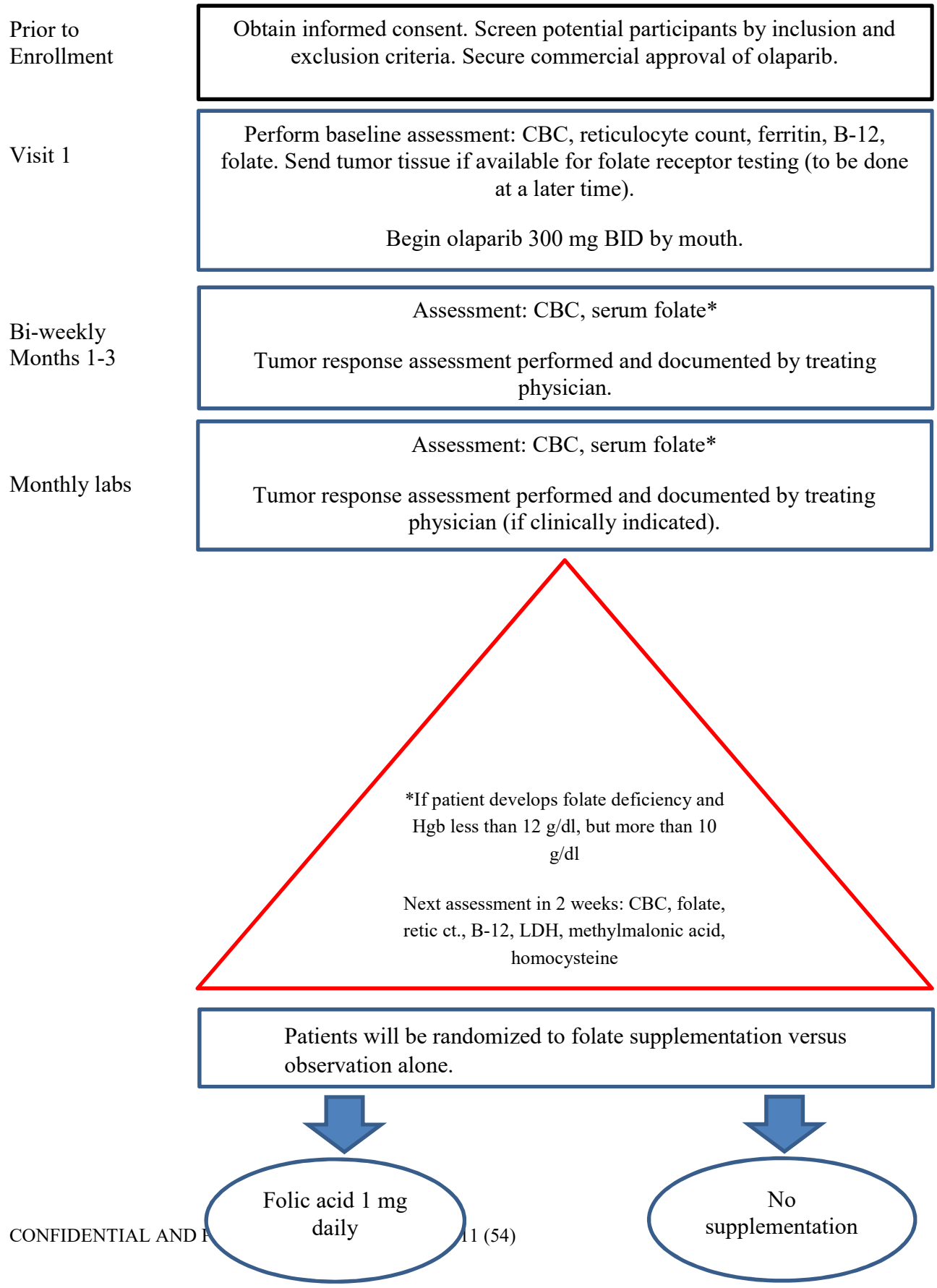
Statistical methods:

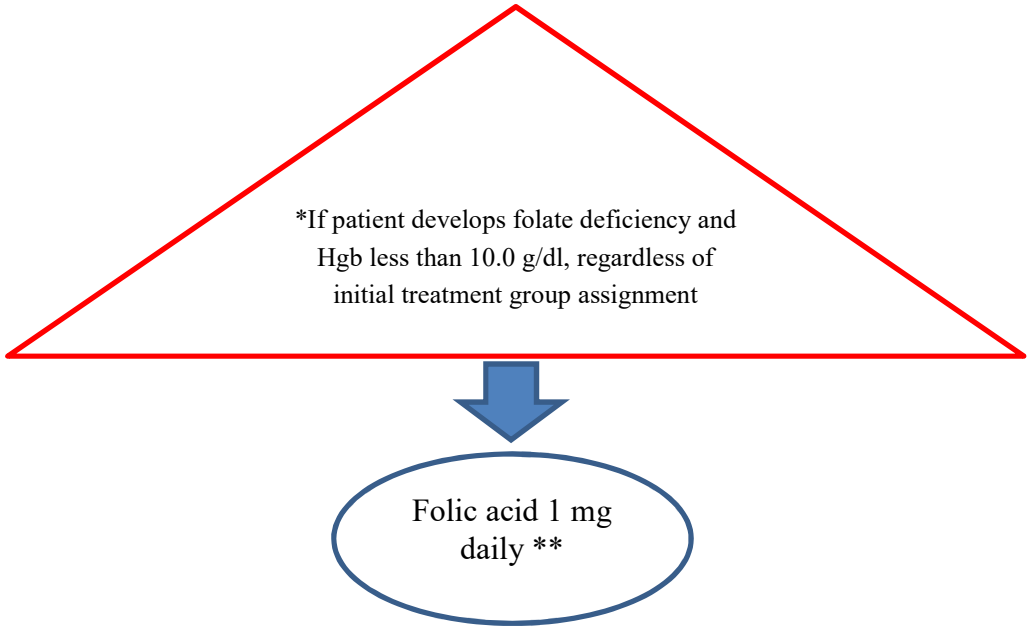
A previous study by Rush investigators observed folate deficiency (<7 ng/mL) in 66% of patients treated with olaparib[2, 3]. Under this framework, a sample size of n=60 is calculated using one-sided test to have 80% power in detecting more than half (50%) of the patients having folate deficiency at 0.05 significance level. Allowing for 20% attrition, we propose a sample size of n=75 for this study. The statistical analysis will provide descriptive summaries of the primary endpoint of drug-induced folate deficiency as well the endpoint of response rate and other secondary endpoints. The significance of the observed percentage of folate-deficient cases will be assessed by statistical hypothesis test, as well as by multivariable analysis of the binary endpoint of folate deficiency adjusted by important covariates. The secondary endpoint of response rate to olaparib will be compared between the group who develop cytopenias, folate deficiency, and receive folic acid supplementation and the comparator group by descriptive summaries as well as by statistical hypothesis test. Statistical analysis will be performed in the R Statistical software. No adjustment for multiplicity will be made. Even though the sample size of 75 is optimal to achieve primary and secondary objectives, it would be reasonable to initially accrue 30 patients and re-evaluate the need for continued accrual based on the percentage of patients who develop folate deficiency in this first phase.

1.3 Schema

The general study design is summarised in Figure 1. Please refer to Schedule of Activities (Section 1.1) for detailed information about the timing of protocol- required blood draws and laboratory tests.

Figure 1 Study design





** If a patient is already on folic acid supplements and continues to experience folate deficiency and Hgb less than 10.0 g/dl, folic acid dose can be increased to 2 mg daily or higher, at the discretion of the investigator. A hematology consultation can be obtained if necessary.

INTRODUCTION

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)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents[4].

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD) [5, 6, 7] such as ovarian cancers in patients with *BRCA*1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

*BRCA*1 and *BRCA*2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo[8, 9] and in the clinic[5]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair[10, 11]. 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.

Initially, olaparib has been FDA approved for the treatment of advanced ovarian cancer [12] . Later, the indications have expanded. Currently, it is approved for the following indications[13 -16]

-First-Line Maintenance *BRCA*m Advanced Ovarian Cancer (g*BRCA*m = germline *BRCA*-mutated or s*BRCA*m = somatic *BRCA*-mutated)

-First-Line Maintenance HRD-Positive Advanced Ovarian Cancer in Combination with Bevacizumab. Homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability.

-Maintenance Recurrent Ovarian Cancer in patients who are in complete or partial response to platinum-based chemotherapy.

-Advanced g*BRCA*m Ovarian Cancer in patients who have been treated with 3 or more prior lines of chemotherapy.

-g*BRCA*m, HER2-Negative Metastatic Breast Cancer

-First-Line Maintenance g*BRCA*m Metastatic Pancreatic Cancer whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen

-HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer in patients with deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone .

Molecular sequencing of the tumor DNA is increasingly used in clinical practice to identify molecularly-targeted agents that can potentially effectively and safely treat patients with advanced cancers. Olaparib is used in this setting when solid tumors harbor molecular alterations such as germline and somatic mutations in *BRCA1* and *BRCA2* genes, other genes in Homologous DNA Recombination pathway, etc[17]. A detailed description of the chemistry, pharmacology, efficacy, and safety of olaparib is provided in the package insert.

1.4 Study rationale

See Section 1.2.

We have observed folate deficiency in 66% of patients of patients with advanced ovarian and metastatic breast cancer occurring within weeks of treatment initiation with olaparib[2, 3]. While folate deficiency is a known cause of macrocytic anemia, it has not been previously reported in association with olaparib therapy. Since macrocytic anemia is a known complication of olaparib treatment regardless of the cancer type treated, folate deficiency can occur in these patients too.

This study is conducted to assess the prevalence and timing of folate deficiency in patients with ovarian, breast, pancreatic, prostate, and other cancers that may benefit from olaparib as determined by their treating physicians based on their tumor sequencing or germline results. .

As folic acid supplementation has not been studied prospectively in this patient population, this study will also evaluate, in a randomized fashion, the impact of folic acid supplementation on anemia and need for transfusion as compared to a placebo group (i.e. no folic acid supplementation while on olaparib).

Background

Olaparib is generally well tolerated. For instance, in the clinical trial of maintenance olaparib monotherapy in patients with platinum-sensitive ovarian cancer who had had 2 or more lines of platinum-based chemotherapy (Study 19), adverse reactions led to olaparib dose interruption, reduction and discontinuation in 35 %, 26 %, and 6 % of patients, respectively[13]. Olaparib is known to cause hematologic toxicity. In the pooled analysis of multiple clinical trials, the following hematologic side effects were observed: anemia in 37% of patients, Macrocytosis (elevated mean corpuscular volume) is reported in up to 89% of patients treated with olaparib[13]. The manufacturer recommends monitoring blood counts at baseline and monthly thereafter, interrupting treatment until any hematologic toxicity has resolved to ≤ grade 1, with additional evaluation if blood counts do not recover after 4 weeks of treatment interruption, including bone marrow and cytogenetic analyses[5, 6]. Little is known about the etiology of olaparib-induced hematologic toxicity.

2. OBJECTIVES AND ENDPOINTS

Primary objective:

To determine the frequency and timing of folate deficiency in patients with solid tumors harboring molecular alterations such as germline and somatic mutations in *BRCA1* and *BRCA2* genes, other genes in Homologous DNA Recombination Repair (HRR) pathway, genomic stability as determined by Homologous Recombination Deficiency (HRD) assay, etc., who are treated with olaparib.

Secondary objectives:

To evaluate the effect of folic acid supplementation on serum folate, hemoglobin level, transfusion needs/number of transfusions, and need for olaparib treatment interruption, dose reduction and drug discontinuation.

To assess response rate (RR) to olaparib as it relates to serum folate level and folic acid supplementation.

To assess progression-free survival (PFS) as it relates to serum folate level and folic acid supplementation.

Exploratory objectives:

To elucidate the mechanism of folate deficiency in patients treated with olaparib including possible interaction with germline *BRCA*1 and *BRCA*2 mutations via testing for folate receptors using immunohistochemistry on available paraffin embedded tumor samples from enrolled patients.

Primary endpoint:

The primary binary endpoint of the study is the percentage of patients who develop drug-induced folate deficiency, defined as serum folate level <7 ng/mL, within three months from start of olaparib therapy.

Secondary endpoints:

To assess the impact of folic acid supplementation on anemia, need for transfusion, and olaparib treatment interruption, dose reduction and drug discontinuation as compared to those who did not receive/require folic acid supplementation

To determine tumor response rate (RR), using treating physician assessment, on olaparib therapy in patients who develop folate deficiency and receive folic acid supplementation as compared to those who do not receive/require folic acid supplementation. Will also compare RR to historical controls (patients with solid tumors treated with olaparib or other approved agents on clinical trials).

To determine progression-free survival (PFS)), using treating physician assessment based on olaparib therapy in patients who develop folate deficiency and receive folic acid supplementation as compared to those who do not receive/require folic acid supplementation. Will also compare PFS to historical controls (patients with solid tumors treated with olaparib or other approved agents on clinical trials) using published data.

Exploratory Endpoints:

To evaluate association between:

- *BRCA* 1, *BRCA* 2, and other HRR gene status (germline mutation carrier vs non-carrier) and the intensity of folate receptor alpha expression in the tumor (<50% or >50%)
- *BRCA* 1, *BRCA* 2, and other HRR gene status (germline mutation carrier vs non-carrier) and nadir serum folate level during olaparib treatment

- *BRCA* 1, *BRCA* 2, and other HRR gene status (germline mutation carrier vs non-carrier) and tumor response in patients receiving folate supplementation as compared to patients not receiving folate supplementation and historical controls
- Folate deficiency and expression of folate receptors in patients' tumor samples

3. STUDY DESIGN

3.1 Overall design

This is a pilot, multi-center study evaluating the prevalence and timing of folate deficiency in patients with advanced solid tumors who are eligible to receive olaparib.

If patients develop folate deficiency concomitantly with a Hgb less than 12.0 g/dl (grade 1), they will then be randomized to receive either a placebo or folate supplementation.

All randomized patients who develop a Hgb less than 10 g/dl (grade 2) concomitantly with folate deficiency will receive folic acid supplementation irrespective of their prior randomization. If such patients were originally randomized to receive folic acid and continue to have a Hgb less than 10 g/dl and folate deficiency despite folate supplementation, folic acid dose will be increased to 2 mg daily or higher at the discretion of the investigator.

Patients will continue with olaparib until objective disease progression (determined by treating physician assessment) as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 5.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 2 Objectives and Endpoints.

3.2 Scientific rationale for study design

See Section 1.2.

3.3 Justification for dose

The dose of olaparib used in this study is 300 mg twice daily which is the currently FDA approved dose. Starting dose modifications based on the patient's medical condition, for example creatinine clearance, are allowed.

3.4 End of study definition

The end of study is defined as 7 months from enrolment. This is to include the one-month follow up physical exam, concomitant medications, adverse effects, and folate level

4. STUDY POPULATION

This study will include all patients with solid tumors who can benefit from olaparib therapy for the treatment of their malignancy as determined by their primary oncologist.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, may be permitted by the principal investigators.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study intervention Patients, who do not meet the entry requirements are deemed as screen failures, refer to Section 5.4.

4.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Capable of providing a signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

3. For inclusion in the optional biomarker research, patients must fulfil the following criteria:

   – Provision of informed consent for biomarker research prior to collection of sample

If a patient declines to participate in the optional biomarker research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

Age

4. Patient must be ≥18 years of age inclusive, at the time of signing the informed consent form.

Type of patient and disease characteristics

Patients with solid tumors harboring molecular alterations which are likely to respond olaparib, such as germline and somatic mutations in *BRCA1* and *BRCA2* genes, other genes in Homologous DNA Recombination Repair (HRR) pathway, genomic stability as determined by Homologous Recombination Deficiency (HRD) assay, etc. Olaparib must be recommended to these patients by their treating physician.

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

   - Haemoglobin ≥ 10 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 of ≥51 mL/min using the Cockcroft-Gault equation or based on a 24 hour urine test :

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

[a] where F=0.85 for females.

7. Eastern Cooperative Oncology Group (ECOG) performance status 0-1).

8. Patients must have a life expectancy ≥ 16 weeks.

9. Patients with measurable and non-measurable disease are eligible.

10. There is no limit on the number of prior therapy lines. Olaparib can be used in the front or a subsequent lines of therapy as well as maintenance.

11. Patients can be enrolled with the lab results outside of the Inclusion criteria range or a performance status = 2, if olaparib is recommended by their treating oncologist/physician and the olaparib Package Insert is followed for dose adjustments.

Sex

12. Female or male

Reproduction

13. Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1.

    Postmenopausal is defined as:

    – Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments

    – Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50

    – radiation-induced oophorectomy with last menses >1 year ago

    – chemotherapy-induced menopause with >1 year interval since last menses

    – surgical sterilisation (bilateral oophorectomy or hysterectomy)

14. Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of olaparib and to not donate sperm during this time.

4.2 Exclusion criteria

Medical conditions

1. Patients with folic acid deficiency, defined as folate <7 ng/mL, or those taking folic acid supplementation within 30 days of olaparib initiation.

2. Other malignancy unless curatively treated with no evidence of disease for ≥5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma. Patients with a history of localised triple negative breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease

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

4. Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML.

5. 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.

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

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

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

9. Patients with known active hepatitis (i.e. Hepatitis B or C).

   – Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible.

   – Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

10. Patients with the history of COVID19 are eligible only after two consecutive negative tests for COVID19.

11. Any exceptions to the eligibility criteria may be discussed with the Principal Investigator on a case by case basis.

Prior/concomitant therapy

12. Any previous treatment with PARP inhibitor, including Olaparib, are allowed.

13. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. Exceptions may be discussed with the Principal Investigator.

14. Patients receiving maintenance Bevacizumab as a single agent prior to the study and /or are planning to receive concomitant Bevacizumab with Olaparib are allowed. Patients who are receiving anti-hormonal therapy or bone protecting agents are allowed. Exceptions may be discussed with the Principal Investigator.

15. Patients who start Olaparib in combination with Bevacizumab are allowed.

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

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

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

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

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

Prior/concurrent clinical study experience

21. Participation in another clinical study with an investigational product administered in the last 1 month

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

23. Patients with a known hypersensitivity to folic acid or any of the excipients of the product.

Other exclusions

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

25. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

26. Previous enrolment in the present study.

27. Breast feeding women.

4.3 Lifestyle restrictions

4.3.1 Meals and dietary restrictions

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

4.3.2 Activity

Contraception

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse .

Men who are sexually active with women of childbearing potential must also agree to the terms listed above.

For details of acceptable methods of contraception refer to Appendix B Acceptable Birth Control Methods.

4.4 Screen failures

Screen failures are defined as patients who signed the informed consent form to participate in the clinical study but are not subsequently entered in the study. Minimal information includes demography, screen failure details, eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

5. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to olaparib and folic acid supplementation.

5.1 Treatments administered

Table 1 Study Treatments

	Treatment 1	Treatment 2
Study treatment name	Olaparib	Folic acid
Dosage formulation	300 mg BID	1 mg daily
Route of administration	Oral	Oral
Dosing instructions	Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.	Folic acid supplementation should be taken at the same time each day, with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Can be taken with or without food.
Packaging and labelling	Study treatment will be prescribed by provider. Each container will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. Olaparib will be commercially supplied.	Study treatment will be prescribed by provider.

If vomiting occurs shortly after the olaparib or folic acid 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.

5.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may dispense study treatment. At site, all study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided.

5.3 Measures to minimise bias: randomisation and blinding

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced

5.4 Treatment compliance

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib and folic acid. Patients will be given a medication calendar to document the olaparib and (if applicable) folate doses taken. Study site staff will review the calendar monthly with the patient and discuss reasons for missed doses, if any. Patients will be instructed to notify study site personnel of missed doses.

Any change from the dosing schedule, does interruptions, dose reductions, and dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the Investigational Medicinal Product (IMP) from receipt by the study site until the destruction or return of all

unused IMP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IMP.

5.5 Concomitant therapy

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

The information on vitamin intake will be collected at the baseline and throughout the duration of the study. Patients will be discouraged to take folate-containing vitamin supplements for at least three months after starting olaparib therapy. However, if they have been on them before the enrolment and decline holding them, they are still eligible to participate.

Anti-emetics/Anti-diarrheals

From screening onwards, should a patient develop nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs (see Section 8.3) and appropriate treatment of the event given.

Medications that may NOT be administered

Table 2 Prohibited medications

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy Radiotherapy (except palliative) Biological therapy Other novel agents	Not permitted while the patient is receiving study medication

*Hormone Replacement Therapy (HRT) is acceptable

*Anti-hormonal agents such as aromatase inhibitors are acceptable.

Restricted concomitant medications

Table 3 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir	Strong or moderate CYP3A inhibitors 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 CRF with the reason documented as concomitant CYP3A inhibitor use.
Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	• Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily 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 150 mg twice daily 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.

Table 3 Restricted concomitant medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Strong inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers 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 then they must be monitored carefully for any change in efficacy of olaparib.
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	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. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

Table 3 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. 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.

5.5.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

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

5.6 Dose modification

Dose Reductions

In case a dose reduction is necessary, the Study treatment will be administered as follows:

Table 4 Dose reductions for olaparib to manage adverse events

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily
250 mg twice daily	200 mg twice daily	150 mg twice daily
200 mg twice daily	150 mg twice daily	100 mg twice daily

Table 5 Dose reduction for olaparib if patient develops moderate renal impairment

Initial Dose	Moderate renal impairment (calculated creatinine clearance by Cockcroft -Gault equation or based on a 24 hour urine test between 31 and 50 ml/min): Dose reduction
300 mg twice daily	200 mg twice daily

If starting dose is 200 mg twice daily, and patient develops renal impairment, dose modification will be determined by the treating physician.

Table 6 Dose reductions for olaparib if patient has to start taking a strong or moderate CYP3A inhibitor

Initial Dose	Strong CYP3A inhibitor	Moderate CYP3A inhibitor
300 mg twice daily	100 mg twice daily	150 mg twice daily

If starting dose is 200 mg twice daily, and patient is required to take a strong or moderate CYP3A inhibitor, dose modification will be determined by the treating physician.

For guidance on dose reductions for management of AEs (including renal impairment) refer to Section 8.4.4.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 6.5.

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 (see Section 8.4.4), or one 150 mg tablet twice daily or one 100 mg tablet twice daily (see Section 6.5).

Folic Acid dose modification:

Patients with folate deficiency will start folic acid supplementation at 1 mg daily. If they continue to have a Hgb less than 10 g/dl (grade 2) and folate deficiency despite folate supplementation, folic acid dose can be increased to 2 mg daily or higher at the discretion of the investigator.

5.7 Treatment after the end of the study

Not applicable - please see Section 4.1 for details of treatment after the study database has been closed.

6. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

6.1 Discontinuation of study treatment

Patients may be discontinued from investigational product (IP) in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)

6.1.1 Procedures for discontinuation of study treatment

The investigator should instruct the patient to contact the site before or at the time if Study treatment is stopped. A patient that decides to discontinue Study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of Study treatment should be documented in the CRF (electronic or paper). All Study treatment should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing Study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Any patient discontinuing investigational product should be seen post discontinuation for the evaluations and sample collections outlined in the study schedule.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Section 7.2).

All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported within 24 hours as described in Section 8.4.1) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study medication to collect and / or complete AE information. For guidance on reporting adverse events after the 30 day follow up period see Section 7.3.2.1.

Discontinuation of Study treatment, for any reason, does not impact on the patient´s participation in the study. The patient should continue attending subsequent study visits and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1 Efficacy assessments

7.1.1 Clinical outcome assessments

Evaluate the percentage of patients who develop drug-induced folate deficiency while on olaparib, defined as serum folate level <7 ng/mL.

Determine the impact of folic acid supplementation on anemia, need for transfusion, and dose modification of olaparib as compared to those who did not receive/require folic acid supplementation.

Tumor assessment will be performed as per treating physician’s decision and would include regular clinical exams, tumor marker monitoring, and imaging (body CT scans) at every 3 -6 month interval. Tumor response will be evaluated according to treating physician assessment. Response rate is defined as achievement of complete response (CR) or partial response (PR). Progression free survival, PFS, is defined as time from enrolment until disease progression or death. Patients who withdrew from olaparib before disease progression or death will be censored at the date of their last tumor assessment.

7.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

7.2.1 Clinical safety laboratory assessments

Table 7 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hgb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Absolute neutrophil count	S/P-Alkaline phosphatise (ALP)
B-Absolute lymphocyte count	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)
B-Mean cell volume (MCV)	S/P-Albumin
	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
Urinalysis (dipstick, if clinically indicated for)	S/P-Urea or Blood Urea Nitrogen (BUN)
U-Hgb/Erythrocytes/Blood	S/P-Total Protein
U-Protein/Albumin	
U-Glucose	

NB. In case a patient shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix A 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

7.2.1.1 Coagulation (if clinically indicated)

· activated partial thromboblastin time {APTT} will be performed if clinically indicated

· international normalised ratio {INR} will be performed if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Each coagulation test result will be recorded in CRF.

7.2.1.2 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 8.4.4.1.3.

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

7.2.2 Physical examinations

Physical exam will be performed and documented at each monthly visit.

7.2.3 Vital signs

Vital signs will be performed and documented at each monthly visit.

7.2.4 Other safety assessments

7.2.4.1 Serum or urine pregnancy test

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

7.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3.

7.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

7.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from time of enrolment throughout the treatment period and including the follow-up period until the last contact.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in CRF.

7.3.2.1 Adverse events after the 30 day follow up period

For Pharmacovigilance purposes and characterisation, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to AstraZeneca Patient Safety 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 (folate), the investigator should notify the Principal Investigator.

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. 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).

7.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAE/non-serious AEs/AEs of special interest, will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Any SAE or non-serious adverse event that is ongoing at the time of the 30-day follow up, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary

7.3.4 Adverse event data collection

The following variables will be collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped

- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (no)
- Action taken with regard to Investigational Product(s)
- AE caused patient's withdrawal from study
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to.
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'
- Description of AE

7.3.5 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in the Clinical Study Protocol.

7.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. 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.

7.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil 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., anaemia versus low haemoglobin 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 unless unequivocally related to the disease under study, see Sections 8.3.9 and 8.3.10.

7.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix A for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

7.3.9 Disease progression

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

7.3.10 New Cancers

The development of a new primary cancer should be reported as an AE (see Section 8.3.13 Olaparib Adverse Events of Special Interest) and would in most cases meet seriousness criteria (with the exception of some non-melanoma skin cancers). 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.

7.3.11 Lack of efficacy

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

7.3.12 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 CRF 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 8.4.1 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 CRF.

Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

7.3.13 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. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

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.

7.4 Safety reporting and medical management

7.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

7.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

7.4.2.1 Maternal exposure

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

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

study medication until 1 month after the last dose of study medication should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

7.4.3 Overdose

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

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

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

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** 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 a SAE, the standard reporting timelines apply, see Section 7.3.2. For other overdoses, reporting must occur within 30 days.

7.4.4 Management of adverse events Dose Reductions

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.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 6.5

7.4.4.1 Management of haematological toxicity

7.4.4.2 Management of anaemia

Table 8 Management of anaemia

Haemoglobin	Action to be taken
Hgb < 10 *but* **≥ 8 g/dl (CTCAE Grade 2)**	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (e.g., 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 Hgb**< 10** *but* **≥ 9 g/dl** investigator judgement to continue olaparib with supportive treatment (e.g., 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 Hgb**< 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).
Hgb < 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 Hgb ≥ 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 Hgb 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 haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 (Hgb less than 8.0 g/dl) or worse anemia and/or development of blood transfusion dependence), refer to guidance later in this section for the management of this.

7.4.4.3 Management of neutropenia, leukopenia and thrombocytopenia

Table 9 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 haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to guidance later in this section for the management of this.

7.4.4.4 Management of prolonged haematological toxicities while on study treatment

If a patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia 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 haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard

haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC gr 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.

7.4.4.5 Management of non-haematological 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 twice daily as a first step and to 200 mg twice daily as a second step (see section 5.6 for more information on dose modification guidance). 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.

7.4.4.6 Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (e.g., dyspnoea) 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.

7.4.4.7 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. 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 (i.e. 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.

7.4.4.8 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 AZ study physician.

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

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 10 Dose reductions for study treatment

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily
250 mg twice daily	200 mg twice daily	150 mg twice daily
200 mg twice daily	150 mg twice daily	100 mg twice daily

7.4.4.9 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 *or* should be reduced to 200 mg twice daily.

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 is it recommended that olaparib be discontinued.

7.5 Biomarkers

Optional samples for biomarker research that should be collected from patients in the study where possible are the following:

- Existing paraffin embedded tissue samples from patients will be collected for assessment of folate receptors via immunohistochemical staining as according to the previously stated Exploratory Objective/Endpoint.

Unless otherwise specified in the protocol, biomarker data will not be routinely reported to sites unless specifically requested. Frequently, biomarker data are generated retrospectively towards the end of the study. Any sample material remaining after completion of analyses to fulfil the study objectives may be used for optional exploratory research to develop methods, assays, prognostics, and/or companion diagnostics related to cancer, disease process, pathways associated with disease state, PARP, and or mechanism of action of olaparib.

7.5.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 10 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical hypotheses

- Olaparib-treated patients develop folate deficiency
- Replacing folic acid in these patients can mitigate olaparib-induced adverse events related to its hematologic toxicity (anemia, transfusion needs/number of transfusions, dose reductions and drug discontinuation)
- Folate replacement does not affect an antineoplastic effect of olaparib

8.2 Sample size determination

A previous study by Rush investigators observed folate deficiency (<7 ng/mL) in 66% of patients treated with olaparib. A sample size of n=60 is calculated using one-sided test to have 80% power in detecting more than half (50%) of the patients having folate deficiency at 0.05 significance level. Allowing for 20% attrition, we propose a sample size of n=75 for this study.

8.3 Populations for analyses

All enrolled patients who receive at least one dose of olaparib will be included in the analysis population to be used to assess the efficacy and safety endpoints.

8.4 Statistical analyses

8.4.1 Efficacy analyses

Patients will be monitored for development of anemia and folate deficiency at scheduled time points throughout the course of the study, as described in Section 1.1. Patients who develop ≤G2 cytopenias and folate deficiency will be randomly assigned in a 1:1 ratio to receive folic acid supplementation 1 mg daily or no supplementation. Patients who develop G3 or higher cytopenias and folate deficiency will be started on folic acid supplementation, thus not included in the randomization. For patients who are randomized, we will assess the impact of folic acid supplementation on anemia, need for transfusion, and dose interruption, dose reduction and drug discontinuation of olaparib as compared to those who did not receive/require folic acid supplementation. Additionally, PFS and RR to olaparib will be compared amongst randomized patients relative to folic acid supplementation.

The statistical analysis will provide descriptive summaries as well as 95% confidence intervals for the primary endpoint of drug-induced folate deficiency in addition to response rate and other secondary endpoints. Kaplan-Meier methodology will be used to estimate the PFS curve and estimate of median PFS and corresponding 95% confidence interval will be provided. The significance of the observed percentage of folate-deficient cases will be assessed by statistical hypothesis test, as well as by multivariable analysis of the binary endpoint of folate deficiency adjusted by important covariates. Covariates will include age, race/ethnic group, previous therapy, Hgb prior to olaparib therapy, genetic testing result (*BRCA* carrier status). RR and PFS will be compared to historical controls as a descriptive comparison. Analyses will be reported on the entire combined cohort of patients with solid tumors and also separately for each cancer type. The statistical analysis of the exploratory endpoint will be specified in the SAP. Statistical analysis will be performed in the R Statistical software. No adjustment for multiplicity will be made.

8.4.2 Safety analyses

Tabulations and descriptive summaries of adverse events (AEs) and serious adverse events (SAEs) will be reported as described in Section 8. Adverse events will be compared among the comparator groups of the study.

8.5 Interim analyses

We consider would be reasonable to initially accrue 30 patients and re-evaluate the need for continued accrual based on the percentage of patients who develop folate deficiency in this first phase.

8.5.1 Data monitoring committee (DMC)

A data monitoring committee will not be utilized for this study. The study will be monitored by the study investigators and information will be shared with the funder company (Astra/Zeneca).

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

A 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 8.4 of the Clinical Study Protocol.

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

The 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 (IP).

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

A 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN 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 ≥ 3 × ULN together **with** TBL ≥ 2 ×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

A 3 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 ≥ 3 × ULN

- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Appendix A 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix A 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

A 4 Follow-up

A 4.1 Potential Hy's Law criteria not met

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

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

A 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.4 Safety Reporting)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the 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 aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

A 5 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 Study Physician contacts the 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 Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

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

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

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

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

- Report an SAE (report term 'Hy's Law') according to 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 amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

A 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to patients with liver metastases 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 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 Appendix A4.

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

A 7 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 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 first on-study treatment visit, as described in Appendix A 6

If **No**: Follow the process described in Appendix A 4.1.

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 Appendix A 4.

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

Appendix B Acceptable Birth Control Methods

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

Women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination [as listed below]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

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 1 month 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 (e.g., 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 (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom