DF/HCC Protocol #: 15-121

Protocol Version Date: July 10, 2017

DF/HCC Biomedical Protocol Template: June 30, 2014

Title: Phase I/II Study of Olaparib and Temozolomide in Patients with Recurrent Small Cell Lung Cancer Following Failure of Prior Chemotherapy

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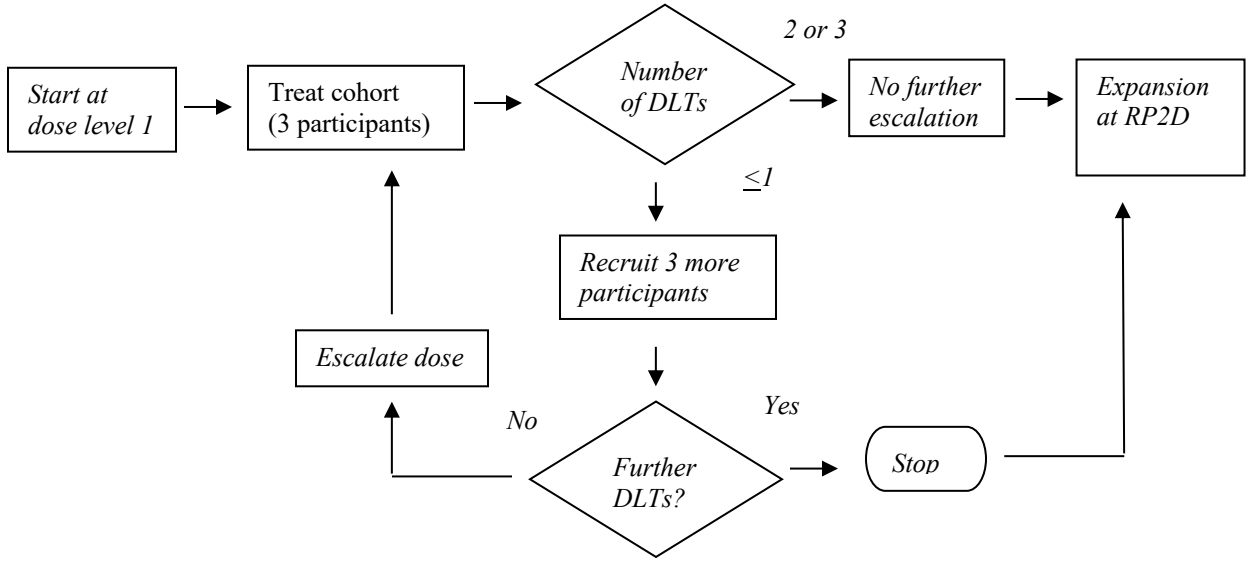
Phase I/II Study of Olaparib and Temozolomide in Patients with Recurrent Small Cell Lung Cancer Following Failure of Prior Chemotherapy

SCHEMA

Phase 1 Portion:



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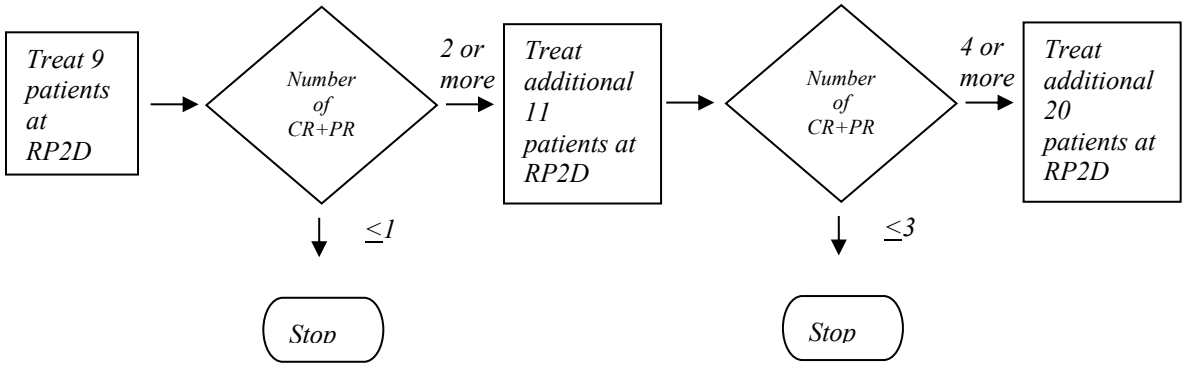

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1. OBJECTIVES

1.1 Study Design

This is a single arm open labeled clinical trial with phase I and phase II portions. The eligibility and exclusion criteria are identical for both portions.

The phase I portion is constructed along a 3 + 3 dose escalation phase I study design, to evaluate the maximum tolerated dose of olaparib (tablet formulation) in adult patients with recurrent small cell lung cancer (SCLC) when administered concurrently with temozolomide. Patients with histologically or cytologically confirmed extensive stage (ES) SCLC that has progressed after one prior course of treatment with platinum-based chemotherapy will be eligible for study participation. Enrollment will begin at a starting dose level of 100 mg olaparib PO BID and 50 mg/m2 temozolomide PO daily, both given days 1-7 of a 21-day cycle. Cohorts of 3 participants each will receive daily dosing of oral olaparib and temozolamide at the starting dose level with plans to dose escalate or de-escalate, depending on whether or not dose limiting toxicities (DLTs) are seen in each cohort. Dose levels will not exceed those defined in Table 2. Optional tumor biopsies, if safe and feasible, will be done within one month prior to study enrollment and after 4-6 weeks of olaparib and temozolomide administration, during the phase 1 portion of the study only. Once the MTD is determined or DLT evaluation of all dose levels has been completed without determination of a MTD, the study will move to the phase II portion at the recommended phase 2 dose (RP2D). All phase II analyses will include patients enrolled in the phase I portion and treated at the RP2D.

In the phase II portion, up to 40 evaluable participants will be enrolled at the RP2D to determine the overall response rate to concurrent olaparib and temozolomide in patients with recurrent SCLC. This portion of the study will also further define safety, toxicity, progression-free survival (PFS) and overall survival (OS). An interim analysis will be performed after 9 patients are enrolled at the RP2D. If < 2 responses (partial or complete) are observed, the study will be terminated. If at least two responses are observed, an additional 11 patients will be enrolled at the RP2D. A second interim analysis will be performed after 20 evaluable patients are enrolled at the RP2D. If at least four responses are observed, an additional 20 patients will be enrolled at the RP2D, with a goal total enrollment of 40 evaluable patients at the RP2D. Tumor assessments will be performed at baseline and repeated every six weeks thereafter to assess disease status. Safety and tolerability will be monitored continuously throughout study participation.

1.2 Primary Objectives

Phase I portion: Determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of combined oral administration of olaparib and TMZ in patients with recurrent SCLC.

Phase II portion: Determine the overall response rate (ORR) to combination olaparib and TMZ in patients with recurrent SCLC.

1.3 Secondary Objectives

Phase I portion:

1. Evaluate the safety and tolerability of combination olaparib and TMZ as defined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
2. Explore variations in MGMT promoter methylation status and poly-ADP-ribose (PAR) levels in tumor biopsy samples obtained before and during treatment.

Phase II portion:

1. Evaluate the safety and tolerability of combination olaparib and TMZ as defined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
2. Measure the time of progression free survival (PFS), and overall survival (OS) in response to olaparib and TMZ therapy.

2. BACKGROUND

2.1 Study Agents

Olaparib

Olaparib (Lynparza, 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. Further details are available in the current olaparib (AZD2281) Investigator Brochure (IB).

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), such as serous ovarian cancers and BRCA1/2 mutated breast cancers, cannot

accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens (Audeh et al., 2010; Tutt et al., 2010). PARP inhibition is also thought to induce cytotoxicity by trapping PARP enzymes to DNA, and in fact PARP inhibition can be more cytotoxic than genetic depletion of PARP (Murai et al., 2012). Levels of poly-ADP-ribose decrease in response to PARP inhibition and this can be used as a pharmacodynamic marker of drug activity (Liu et al., 2008). Olaparib was granted accelerated approval by the U.S. Food and Drug Administration in December 2014 for women with advanced ovarian cancer associated with defective BRCA genes.

Pre-clinical experience

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

Toxicology and safety pharmacology summary

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

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

Clinical experience

Emerging safety profile

This section lists those events that are to be regarded as expected for regulatory reporting purposes.

Although most of the clinical data for safety and toxicities of olaparib as described below were collected using the capsule formulation, the tablet formulation used in the current protocol appears to be generally well tolerated, including in patients with Ewing's sarcoma at 400 mg BID, as monotherapy.

Administration of olaparib has been associated with reports of laboratory findings and/or clinical diagnoses of:

- Hematological toxicity:
  - Anemia, generally mild or moderate (CTCAE Grade 1 or 2)
  - Neutropenia, predominantly mild or moderate (CTCAE Grade 1 or 2)
  - Lymphopenia, generally mild or moderate (CTCAE Grade 1 or 2)

- Thrombocytopenia, generally mild or moderate (CTCAE Grade 1 or 2) sometimes severe (CTCAE Grade 3 or 4)
- Mean corpuscular volume elevation

- Nausea and vomiting, generally mild or moderate (CTCAE Grade 1 or 2), intermittent and manageable on continued treatment
- Decreased appetite, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Diarrhea, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dyspepsia and upper abdominal pain, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dysgeusia, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Fatigue (including asthenia) generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Headache, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Dizziness, generally mild or moderate intensity (CTCAE Grade 1 or 2)
- Stomatitis, generally mild or moderate intensity (CTCAE Grade 1 or 2)

Important potential risks:

- Pneumonitis events with no consistent clinical pattern have been reported in a small number (<1%) of patients receiving olaparib
- Myelodysplastic syndrome/AML have been reported in a small number (<1%) of patients receiving olaparib with extensive previous exposure to chemotherapy
- New primary malignancies have been reported in a small number of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases.

These events will continue to be monitored to assess frequency and severity as patient exposure increases. These events suggest an emerging safety profile for olaparib that supports further studies in cancer patients.

Temozolomide

Temozolomide is an oral alkylating agent and an imidazotetrazine derivative of dacarbazine, with FDA approval for use in patients with newly diagnosed glioblastoma multiforme (GBM) or refractory anaplastic astrocytoma. In newly diagnosed GBM, temozolomide is administered at 75 mg/m2 for 42 days concomitantly with radiotherapy, and then at a maintenance dose of 150 mg/m2 days 1-5 of a 28-day cycle for 6 cycles. In refractory anaplastic astrocytoma temozolomide is administered at an initial dose of 150 mg/m2 once daily for 5 consecutive days of a 28-day cycle. Adverse reactions can include myelosuppression, myelodysplastic syndrome, Pneumocystis Pneumonia, and hepatotoxicity. The most common adverse reactions (≥10% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia and insomina. The most common grade 3-4 hematologic laboratory abnormalities (≥10% incidence) that have developed during treatment with temozolonmide are: lymphopenia, thrombocytopenia, neutropenia and leukopenia.

Combination Olaparib and Temozolomide

Khan et al. (2011) demonstrated, in a phase I study, that dacarbazine can be used in combination with 100mg BID dosing of oral olaparib (capsule formulation), given for 7 days every 21 day cycles. Dose-limiting toxicities were neutropenia and thrombocytopaenia. Currently, a phase I study of olaparib with temozolomide in patients with glioblastoma is underway in the United Kingdom and a phase I study of olaparib (tablet formulation) with temozolomide in patients with relapsed Ewing's sarcoma is underway at the Dana-Farber/Harvard Cancer Center in Boston, USA (NCT01858168). The study described in the current protocol evaluates olaparib with temozolomide in patients with relapsed extensive stage SCLC. Further information on temozolomide product information is publicly available and provided by the FDA.

Starting Dose

The starting doses of olaparib (tablet formulation), to be administered twice daily, and temozolomide, to be administered once daily every evening, on days 1 through 7 of a 21-day cycle, is determined based on prior knowledge of the ongoing trials in glioblastoma and Ewing's sarcoma (NCT01858168) using combination olaparib and temozolomide. As of July 2014, NCT01858168 was enrolling at the *fourth* dose level: 200 mg olaparib (tablet formulation) PO BID and 75 mg/m2 PO daily temozolomide, dosed days 1-7 of a 21-day cycle. We will plan to start at doses equivalent to the *second* dose level in NCT01858168 (100 mg olaparib PO BID and 50 mg/m2 PO daily temozolomide dosed days 1-7 of a 21-day cycle), conservatively estimating that toxicities may be more severe in ES-SCLC patients who are generally older and may be more heavily pre-treated than patients with advanced Ewing's sarcoma.

2.2 Small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related mortality in the United States. Small cell lung cancer (SCLC) is a high-grade neuroendocrine subtype that accounts for 14% of all lung cancers in the United States (American Cancer Society, 2014). SCLC is predominantly associated with a heavy tobacco history. Molecularly, nearly all SCLCs have inactivation of two tumor suppressor genes, *Tp53* and *Rb1* (Rudin et al., 2012; Peifer et al., 2012). Clinically, SCLC has traditionally been staged according to the Veterans Administration Lung Study Group staging system as limited stage (LS) or extensive stage (ES). Using the AJCC v7 lung cancer staging system, LS disease is equivalent to $T_{any}N_{any}M0$ and confined to one tolerable radiation port, and ES disease is equivalent to $T_{any}N_{any}M1$ or extending beyond a tolerable radiation port. Approximately 1/5 of SCLC patients present with limited stage disease and the remaining patients present with extensive stage disease. LS-SCLC is managed with combination chemotherapy and radiation, with a 5-year overall survival of roughly 20-30%. ES-SCLC is managed with chemotherapy alone. The NCCN Guidelines recommend treating ES-SCLC with 4 to 6 cycles of cisplatin or carboplatin in combination with etoposide or irinotecan. Although response rates to first-line therapy are 44-69%, disease invariably relapses with 2-year survival of less than 10% (Jackman and Johnson, 2005).

Despite single agent activity of a number of chemotherapy agents in SCLC, topotecan is the only drug FDA-approved specifically for this indication. A phase II single-arm study of topotecan 1.5 mg/m^2/d IV days 1-5 of a 21-day cycle in patients with relapsed SCLC demonstrated an overall response rate (ORR) of 21.7% (Ardizzoni et al., JCO 1997). For patients with refractory disease (recurrence within 3 months of finishing chemotherapy), response rate (RR) was 6.4% (3 of 47 patients; 95% CI 1.3% to 17.6%), and for patients with sensitive disease (recurrence more than 3 months from finishing chemotherapy) RR was 37.8% (17 of 46 patients; 95% CI 23.8% to 59.5%). A subsequent randomized phase III trial comparing oral topotecan to IV topotecan showed that these regimens have comparable response rates and median overall survival in patients who had a partial or complete response to first-line therapy with recurrence at least 90 days after first-line chemotherapy. The response rates were 18.3% and 21.9% with oral and IV topotecan, respectively. A randomized phase III study of oral topotecan (2.3 mg/m^2/d days 1-5 of a 21-day cycle) versus best supportive care (BSC) in patients with relapsed SCLC showed a superior median survival of 25.9 weeks (95% CI 18.3 to 31.6) with topotecan versus 13.9 weeks (95% CI 11.1 to 18.6) with BSC (O'Brien et al., 2006). The adjusted hazard ratio (HR) for overall survival was 0.61 (95% CI 0.43 to 0.87).

Temozolomide also has activity in relapsed ES-SCLC (Pietanza et al., 2012). A phase II single-arm study of temozolomide 75 mg/m2/d days 1-21 of a 28-day cycle in patients with relapsed ES-SCLC after 1or 2 prior regimens demonstrated an ORR of 20% (95% CI 11%-32%). ORR was 23% (95% CI 12%-37%) in the cohort with sensitive disease (relapse >=2 mo after first-line therapy) and 13% (95% CI 2% to 38%) in the cohort with refractory disease (relapse <2 months after first-line therapy). Single-agent temozolomide was well-tolerated. 6% of patients experienced grade ≥3 nonhematologic toxicity (3% fatigue, 3% rash/desquamation, all grade 3). Grade ≥3 hematologic toxicity included anemia (3%), thrombocytopenia (10%), leukopenia (4%), lymphopenia (30%), neutropenia (5%) and febrile neutropenia (2%) as well as two cases of MDS (3%). There were no treatment-related deaths. Responses were higher among cases with methylated MGMT promoter than those with unmethylated *MGMT* promoter (38% vs 7%, p=0.08).

2.3 Rationale

The scientific rationale for this study arises out of published laboratory observations and early clinical experience.

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 monotherapy or in combination with established chemotherapies. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment. In a phase I study of olaparib in a BRCA1/2 enriched population, 12 of 19 BRCA carriers had either radiological or tumor-marker responses or meaningful disease stabilization, with 9 showing response by RECIST (Fong et al., 2009). In a phase II setting, olaparib at 400mg BID had an ORR of 33% in BRCA1/2 carriers with recurrent ovarian cancer (Audeh et al., 2010) and 41% in BRCA1/2 carriers with advanced breast cancer (Tutt et al., 2010).

In SCLC cell lines, PARP1 is highly expressed, and PARP inhibition potently reduces viability of cell lines (Byers et al., 2012). In a panel of solid tumor cell lines, PARP inhibition acts synergistically with temozolomide to inhibit growth (Delaney et al., 2000). Furthermore, PARP inhibition acts synergistically both with cisplatin plus etoposide and with irinotecan to reduce cell viability (Byers et al., 2012). In xenograft models, single agent PARP inhibitor BMN 673 significantly reduces tumor growth compared to vehicle, and is equivalent or slightly more potent than weekly cisplatin (Cardnell et al., 2013). Interestingly, inactivation of the tumor suppressor gene *Rb1* is a hallmark genetic event in SCLC (Peifer et al., 2012; Rudin et al., 2012), and results in increased activity of the transcription factor E2F1. PARP1 cooperates with E2F1 to regulate DNA repair enzymes (Simbulan-Rosenthal et al., 1999; Simbulan-Rosenthal et al., 2003). Therefore, the inhibition of PARP1 could disrupt DNA repair both directly, by

disrupting repair of double stranded DNA breaks, and indirectly, by reducing expression of E2F1-regulated DNA repair proteins.

Clinical trials are underway to test the activity of PARP inhibitors in patients with SCLC. An ECOG trial is assessing the PARP inhibitor veliparib (ABT-888) in combination with cisplatin and etoposide as first-line treatment in SCLC; the phase I portion of the study is complete and phase II is underway. This study established a MTD of Veliparib 100 mg BID D1-7 in combination with cisplatin (75 mg/m2 on D1) and etoposide (100 mg/m2 on D1-3) in a 21-day cycle [ASCO 2014 abstract 7023]. 9 patients were enrolled and there was one DLT at the 100 mg dose (grade 5 cardiac failure). Unconfirmed investigator-assessed efficacy outcomes in 7 patients were stable disease in 2/7, partial response in 4/7 and complete response in 1/7. BMN673, a newer highly potent PARP inhibitor, is being studied as a single agent in patients with relapsed platinum-sensitive SCLC. A phase I dose escalation study established an MTD of 1 mg/d. Dose-limiting thrombocytopenia occurred in 1/6 and 2/5 patients at 900 ug/d and 1100 ug/d, respectively. Partial responses were observed in 2 of 20 SCLC patients treated [ASCO 2014, abstract 7022]. A randomized placebo-controlled phase II study of olaparib as maintenance therapy in patients with SCLC who have completed first-line chemotherapy with cisplatin and etoposide is underway in the United Kingdom and has not yet been reported.

Phase 1 experience

As of February 6, 2017, 13 subjects have been enrolled to the phase 1 portion of this study. Three subjects each were enrolled to dose levels 1, 2 and 4, while four subjects were enrolled to dose level 3, as one discontinued study during the DLT-monitoring period and therefore was replaced per protocol. None of the 13 subjects treated to date experienced a DLT. Although DLT criteria were not met in the DLT-monitoring period, grade 3 adverse events that were considered possibly or definitively related to study drugs were observed outside of the DLT-monitoring period. No grade 3 AEs occurred among the three subjects in dose level 1, who remained on study for 5.6, 7.6 and 2.9 months. Among subjects treated at dose level 2, one subject experienced grade 3

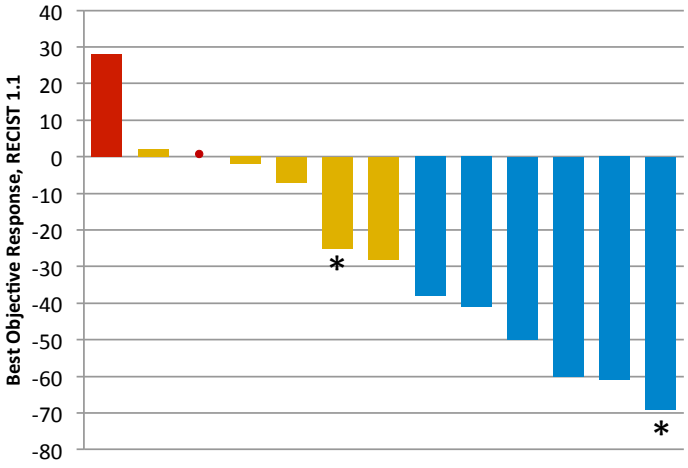

Figure 1. Best objective responses. Best objective responses using RECIST 1.1 criteria are shown in waterfall plot. Partial responses are shown in blue, stable disease in yellow, and progressive disease in red. There was one patient with PD with 0% response by RECIST measurements (red circle). At the time of data cutoff, two patients (*) continued on therapy.

lymphopenia, one subject experienced grade 3 thrombocytopenia, and one subject experienced grade 3 neutropenia. At dose level 3, grade 3 neutropenia occurred in all of the 3 subjects who remained on study for greater than one cycle. Additionally, 2 subjects experienced grade 3 anemia and 1 subject experienced grade 3 thrombocytopenia. At dose level 4, 1 subject experienced grade 3 neutropenia, 1 subject experienced grade 3 anemia, and 1 subject experienced grade 3 emesis. There were no grade 4 or 5 related events or SAEs in the phase 1 portion of the study.

Dose reductions occurred for patients who started at dose levels 3 and 4. Of the three DLT-evaluable patients who enrolled at dose level 3, one ultimately reduced to dose level 2 and 2 ultimately reduced to dose level 1. Reasons for dose reductions in this cohort included grade 2 thromobocytopenia and grade 3 neutropenia in one patient; grade 3 anemia in one patient; and grade 3 thrombocytopenia and grade 3 anemia in one patient. Of the 3 patients who enrolled at dose level 4, one ultimately reduced to dose level 3, one to dose level 2 and 1 to dose level 1. Reasons for dose reductions in this cohort included grade 2 thrombocytopenia in one patient, grade 3 vomiting in one patient, and grade 2 anemia, grade 2 thrombocytopenia and grade 2 neutropenia in one patient.

The best objective response for all 13 registered participants is shown in Figure 1 and summarized in Table 1. There were 6 partial responses, all confirmed on at least one subsequent scan at least 4 weeks following the prior. Responses were seen at all dose levels. There were 5 participants with stable disease and two with progressive disease. There were no complete responses. At the time of data cut-off, two participants remained on study. The median progression free survival (mPFS) was 5.6 months. The median duration of therapy (mDOT) was 5.0 months. The median duration of response (mDOR) among the 6 responders was 3.4 months.

Best response	Dose level 1	Dose level 2	Dose level 3	Dose level 4	**All dose levels (%)**
PR	2	1	2	1	6 (46)
SD	1	1	1	2	5 (38)
PD	0	1	1	0	2 (15)
mPFS months (range) (N=13)	5.6 (2.1-N/A)				
mDOT months (range) (N=13)	5.0 (0.1-11.6)				
mDOR months (range) (N=6)	3.4 (2.8-N/A)				

Table 1. Efficacy in phase 1 portion of the study, data cut-off February 6, 2017.

2.4 Correlative Studies Background

In small cell lung cancer, the methylation status of the *MGMT* promoter may serve as a biomarker for sensitivity to temozolomide. Among SCLC patients treated with temozolomide, those with methylated *MGMT* promoter had a higher response rate than those with unmethylated MGMT promoter (Pietanza et al., 2012). Presently, biomarkers or predictors for response to PARP inhibition are not well defined. However, levels of poly-ADP ribose (PAR) can be used to assess PARP activity and inhibition. Activated PARP enzymes trigger polymerization of ADP-ribose at sites of DNA damage, leading to elevated levels of PAR in cells. Measurement of PAR levels using a well-validated enzyme linked immunosorbent assay (ELISA) can be used to assess PARP inhibitor activity (Liu et al., 2008).

Therefore, an exploratory study analyzing tumor tissue for *MGMT* promoter methylation status and PAR levels may be informative. We plan to study tumor tissue obtained prior to olaparib and temozolomide administration and at 4-6 weeks after initiation of olaparib and temozolomide. Optional tumor biopsies will be performed to obtain pre and post treatment tissues and cells for biomarker tests. All tissues obtained will be analyzed by standard pathology procedures to assess histological parameters including proliferation rate, apoptosis, and necrosis. Additional markers for more detailed pathway analysis may also be utilized depending on the availability of sufficient material, specific findings during the study, and developments in this rapidly advancing field of research. The techniques used may include RNA analysis (including expression and RNA sequencing) and DNA analysis (including specific gene sequencing, whole exome sequencing, and whole genome sequencing), immunohistochemistry (IHC), and immunofluorescence (IF). In addition, isolated live tumor cells may be grown *in vitro* and/or in mouse xenograft models, as a means to develop a resource for ongoing comparative analyses of SCLC tumors pre- and post-treatment and for performing functional assays. We believe that the combination of these approaches will be essential to obtain a complete picture of the determinants of response to these targeted therapies and possible mechanisms of resistance. Importantly, such studies are significantly lacking in SCLC, as surgical resection at the time of diagnosis is rare and re-biopsy is not routinely performed. Due to budget limitations, tumor biopsies will be offered during the phase 1 portion of the study but not during the phase 2 portion of the study.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Patients must meet the following criteria on screening examination to be eligible to participate in the study. The eligibility criteria apply to both the phase I and phase II portions of the study.

1. Participant must have histologically or cytologically confirmed small cell lung cancer and may not be a candidate for potentially curative therapy.
2. Presence of measurable disease (RECIST 1.1): At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.
3. The small cell lung cancer must have progressed radiographically following a platinum-based (cisplatin and/or carboplatin) standard prior chemotherapy regimen. Any number of interval prior lines of therapy is allowed. Patients who have received prior platinum-based chemotherapy and radiation for limited stage SCLC and have subsequently developed relapsed disease are eligible, as long as the platinum-based therapy was given within 12 months prior to the time of relapse.
4. Participant *(male/female)* must be ≥ 18 years of age.
5. Participant must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
   - Hemoglobin ≥ 10.0 g/dL and no known active bleeding.
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - White blood cells (WBC) > 3 x 10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal (unless liver metastases are present in which case it must be ≤ 5x ULN)
   - Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN)
6. ECOG performance status 0-1
7. Participant must have a life expectancy ≥ 16 weeks.
8. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days of initial dose of olaparib and temozolomide AND must agree to the use of two highly effective forms of contraception (see Section 5.5) throughout their participation in the study and for at least 3 months after the last dose of olaparib and temozolomide, OR confirmed prior to treatment on day 1 to be postmenopausal or surgically sterile.

   Postmenopausal is defined as:
   - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments,
   - LH and 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, or surgical sterilisation (bilateral oophorectomy or hysterectomy).

9. Participant is willing to comply with the protocol for the duration of the study, and undergo treatment and scheduled visits and examinations including follow up. Participant must obtain prior approval from insurance to reimburse for oral temozolomide for the duration of the study or agree to self-pay for oral temozolomide.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study. The exclusion criteria apply to both the phase I and phase II portions of the study.

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. Previous enrollment in the present study.
3. Participation in another clinical study with an investigational product during the 21 days prior to first dose of olaparib and temozolomide.
4. Participants receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment with olaparib and temozolomide.
5. Participants are to discontinue the use of the following classes of inhibitors of CYP3A4. Patients who are on these drugs are eligible if a washout period of a minimum of 7 days occurs before start of olaparib and temozolomide.
   - Azole antifungals
   - Macrolide antibiotics
   - Protease inhibitors
6. Persistent clinically significant toxicities (>=CTCAE v. 4.0 grade 2) caused by previous cancer therapy, with the exception of alopecia.
7. Participants with a previously documented diagnosis of myelodysplastic syndrome (MDS) (or any dysplastic leukocyte morphology suggestive of MDS) or acute myeloid leukaemia.
8. Participants with symptomatic uncontrolled brain metastases. Baseline brain imaging by CT or MRI is required for all patients. Participants with brain metastases that have been treated with prior radiation therapy and are stable on a subsequent scan are allowed. Participants with untreated possible brain metastases that are new at the time of screening and are < 1 cm and asymptomatic are allowed. The participant can receive corticosteroids as long as these were started and at a stable dose at least 28 days prior to treatment.

9. Major surgery within 14 days of starting study treatment and patients must have recovered from any effects of any major surgery.
10. Participants 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, QTc prolongation > 470 msec, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression (untreated and unstable for at least 28 days prior to study entry), extensive bilateral lung disease with less than 20% predicted lung function by DLCO (Lung Diffusion Capacity Testing), or any psychiatric disorder that prohibits obtaining informed consent.
11. Participants unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
12. Pregnant or Breast feeding women. All patients (male and female) must agree to practice a medically acceptable method of contraception as defined in section 5.5. Should a woman become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately.
13. Patients who have a history of and are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy. Baseline testing is not required.
14. Patients with known active Hepatitis B or C. Baseline testing is not required.
15. Patients with a known hypersensitivity to olaparib, temozolomide or any of the excipients of the products.
16. Patients with uncontrolled seizures.
17. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated with no evidence of disease for ≥ 5 years.
18. Patients with current and symptomatic pneumonitis, or extensive bilateral lung disease on high resolution CT scan.
19. Patients with whole blood transfusion in the last 120 days prior to entry to the study.
20. Patients with previous allogeneic bone marrow transplant.
21. Patients with active, uncontrolled infection.
22. Patients who need to continue treatment with any prohibited medications listed in Section 5.6
23. Patients who have not completed the appropriate washout period for the prohibited medications in Section 5.6

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

This study is open to all subpopulations of patients as long as they fulfill eligibility criteria.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration(SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Participating Institutions

Not applicable

4.4 Registration Process for Other Participating Institutions

Not applicable

5. TREATMENT PLAN

The Investigational Products Supply (IPS) section of AstraZeneca will supply olaparib to the investigational drug pharmacy at the MGH Cancer Center as tablets.

Temozolomide will be obtained through a pharmacy as the commercial product. As stated in section 3.1, only participants with insurance approval to obtain temozolomide or who agree to self-pay for oral temozolomide will be able to participate in this study. They will be prescribed up to a 21 day supply of temozolomide (to provide enough temozolomide for up to three cycles of treatment) once they sign ICF and are determined to be eligible. C1D1 will begin only when a supply of temozolomide is in the participant's possession.

Investigational product	**Dosage form and strength**	**Manufacturer**
olaparib [a]	25 and 100 mg tablets	100 mg manufactured by AbbVie 25 mg manufactured by AbbVie and AstraZeneca
Commercial product	**Dosage form and strength**	**Manufacturer**
temozolomide	5, 20, 100, 140, 180, and 250 mg capsules	Merck

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

Dose Levels (given days 1-7 of every 21 days)	**Olaparib**	**Temozolomide (rounded to nearest 5 mg)**
-3	25 mg BID	25 mg/m2 QD
-2	50 mg BID	25 mg/m2 QD
-1	50 mg BID	50 mg/m2 QD
1 **	100 mg BID	50 mg/m2 QD
2 (patients enrolled before 07/07/17)	100 mg BID	75 mg/m2 QD
2A (patients enrolled after 07/07/17)	200 mg BID	50 mg/m2 QD
3	200 mg BID	75 mg/m2 QD
4	200 mg BID	100 mg/m2 QD

Table 2. Dose levels. For patients enrolled after July 7, 2017, dose level 2A will replace dose level 2 for necessary dose reductions.

** Starting dose level

Definition of Dose-Limiting Toxicity

Individual participant safety will be assessed by following adverse events (AEs), and physical and laboratory examinations from the time the participant receives the first dose of olaparib and temozolomide until 30 days after the participant's last administration of olaparib and temozolomide.

Dose-limiting toxicity (DLT) is based on the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). Only participants enrolled in the phase I portion will be evaluated for DLTs. Participants who experience a DLT during the DLT-determining period will stop study drugs and will be followed for resolution. If the DLT resolves to grade ≤ 1 in ≤ 7 days then the participant may restart study drugs and continue on study with dose modification as per section 6.3 and with the approval of the principal investigator. If the DLT does not resolve with the above specifications, then the participant

will undergo an exit study as per section 5.2.6, and will be followed for resolution of any toxicities as per section 5.8.

A DLT will be defined as any of the following events possibly, probably, or definitely related to olaparib and/or temozolomide, and occurring during days 1-21 of the study after initiating study drug dosing. Participants will be eligible for DLT evaluation if they are enrolled in the phase I portion of the study and complete administration of all doses of study drugs during days 1-21.

- Grade 4 neutropenia (absolute neutrophil count < 500/μL) lasting > 7 days or if myeloid growth factor (i.e. GCSF) is clinically required
- Grade 3 febrile neutropenia lasting > 7 days
- Grade 4 febrile neutropenia
- Grade 3 thrombocytopenia (platelet count < 50,000/ μL) or grade 4 thrombocytopenia (platelet count < 25,000/ μL) with clinically significant bleeding or lasting > 7 days
- Grade 4 anemia lasting > 7 days
- Grade ≥ 3 vomiting not controlled within 72 hours by maximal supportive care with antiemetic therapy.
- Any Grade ≥ 3 non-hematologic toxicity excluding:
    - grade 3 electrolyte abnormalities that are asymptomatic and resolve in ≤ 7 days
    - grade 3 nausea that resolves in ≤ 7 days
        - Failure to restart both olaparib and temozolomide administration within 2 weeks of the first missed dose when drug is withheld for Grade ≥ 3 AE
- Delay of cycle 2 day 1 for > 2 weeks due to an AE
- Unexpected Aes of grade 4 or higher will be determined by the Principal Investigator and the DF/HCC Data and Safety Monitoring Committee.

Lymphopenia is an anticipated toxicity and is not considered a DLT at any grade.

Dose escalation and/or de-escalation in the phase I portion of this trial will proceed within each cohort according to the following table:

Number of Participants with DLT at a Given Dose Level	**Escalation Decision Rule**

0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Enough participants will be entered at the next lowest dose level as necessary until a total of 6 have been administered olaparib and temozolomide at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Enough participants will be entered at the next lowest dose level as necessary until a total of 6 have been administered olaparib and temozolomide at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the maximum tolerated dose (MTD). At least 6 participants will be administered olaparib and temozolomide at the MTD.

Table 3. Dose escalation and de-escalation plan for the phase 1 portion.

Olaparib and temozolomide dose escalation will not exceed the dose levels shown in Table 2. If an MTD is established, the MTD will be the RP2D. If a MTD is not established after enrollment and DLT evaluation at dose level 4 has been completed, then a RP2D which will be determined by the principal investigator with approval by AstraZeneca.

Once a RP2D is established, additional subjects will be enrolled at the RP2D as part of the phase II portion of the study (as stated in section 14).

Recommended Phase 2 Dose

The Phase 1 experience as of February 6 2017 is summarized above in section 2.3. The grade 3 AEs observed in cycles 2 and beyond at higher dose levels suggest that myelosuppression will be a major obstacle for treating patients at higher doses, and that at dose level 4 GI toxicity also becomes more pronounced. Nonetheless, activity of combination olaparib and temozolomide in SCLC is observed at all dose levels. Based on this phase 1 experience, it is the recommendation of the principal investigator that the phase 1 portion of the study should not continue dose escalation beyond the originally proposed

4 dose levels, and that phase 2 portion should proceed at a RP2D of olaparib 200 mg PO BID and temozolomide 75 mg/m2 PO daily days 1-7 of a 21-day cycle, corresponding to dose level 3.

5.1 Pre-treatment Criteria

Prior to any study related testing, patients will sign the informed consent form and undergo medical evaluation to establish their baseline condition and determine eligibility. Imaging and all other studies will be obtained within 28 days of enrollment for the purpose of baseline assessment:

Complete medical history and physical examination including:

- Complete medical history
- Documentation status of disease
- Documentation of prior systemic therapies for advanced disease treatment
- Documentation of current medications and all medications used within 30 days prior to enrollment.
- Complete physical examination, including vital signs (pulse, blood pressure, weight, and height) and assessment of ECOG performance status (See Appendix A)
- Pre-existing conditions will be assessed and evaluated according to the NCI CTCAE v4.0 to establish the patient's baseline condition

Disease-Specific Laboratory Tests - Pathology and Tumor Imaging

- Review of pathologic diagnosis
- Subjects enrolled to the phase 1 portion of the study who initially consented will undergo an optional tumor biopsy prior to olaparib and temozolomide administration, if the biopsy is deemed to be low risk by the investigator. Patients may refuse the optional biopsy procedure at the time of biopsy timepoint.
- Baseline tumor imaging studies of the chest, abdomen and pelvis will be obtained with CT or MRI, and baseline tumor imaging studies of the brain will be obtained either by CT or MRI. The modality or modalities chosen for any individual patient will be the same throughout the duration of the study. Repeat tumor assessments will be perfomed at 6 weeks, 12 weeks and every 6 weeks thereafter to assess response and disease progression. Repeat brain imaging may be performed at the discretion of the investigator.

The following screening laboratory tests will be performed within 28 days prior to Day 1 of treatment

- CBC with differential
- Chemistries: sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]
- INR and APTT
- Urinalysis
- Urine or serum pregnancy test (for premenopausal women)
- ECG

5.2 Schedule of Drug Administration and Monitoring

5.2.1 Visit 1 (Day 1)

Patients who have signed the informed consent form, completed the screening process, and met the criteria for enrollment will be entered into the trial and assigned an identification number. In addition the following will be performed:

- Certification that patient meets all inclusion and exclusion criteria and is able to comply with all requirements of the clinical trial
- Review concomitant medications since screening
- Perform physical examination with vital signs and ECOG performance status
- Blood investigations – to be done if screening labs were done more than 7 days prior to Day 1. Patient will wait for the lab results on this day to re-confirm lab parameters for eligibility.
    - CBC with differential
    - Chemistries: sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]
    - Urine or serum pregnancy test (for premenopausal women)

The above laboratory test results will be reviewed to confirm that the participant meets eligibility criteria again before olaparib is given out. (Temozolomide is not provided by the clinical trials pharmacy.) Dose calculation is based on weight/BSA (using Dubois formula) within 28 days of the day the participant receives olaparib and temozolomide. If the weight on cycle 1 day 1 has changed by >10% compared to the weight used to calculate the temozolomide dose, then the temozolomide dose should be recalculated and temozolomide should be re-prescribed based on the current weight. If the weight on cycle 1 day 1 has changed by ≥ 5% compared to the weight used to calculate the temozolomide dose, then the temozolomide dose may also be recalculated and temozolomide re-prescribed based on the current weight, at the investigator's discretion. Study agents and a drug diary will be supplied to the patient on the day 1 of study and given dosing instructions as per section 5.3.

Safety Labs: Day 1 labs of all cycles and Day 4 labs

Subjects with grade ≥2 ALT, AST or total bilirubin level on day 1 of any cycle should have labs (comprehensive metabolic panel, CBC with differential) checked on day 4. If any new grade ≥3 lab abnormalities or grade ≥2 blood bilirubin increase is present on day 4, the subject should discontinue treatment for the remainder of the cycle, and the case should be discussed with the Principal Investigator to determine subsequent dosing.

In addition, labs including comprehensive metabolic panel and CBC with differential can be checked at any time point at the investigator's discretion if there is concern for thrombocytopenia, leukopenia, anemia, or any other clinically relevant alterations.

5.2.2 4-6 weeks after initiation of olaparib and temozolomide

Study participants will undergo an optional biopsy of a target lesion, if the biopsy is deemed to be low risk by the investigator. At the time of biopsy, participant will repeat CBC with differential, Chemistries, and Coagulation tests. Optional tumor biopsies will be offered during the phase 1 portion of the study only.

5.2.3 Visit 2-4 (Day 8, 15, 22)

- Review of concomitant medications and treatment history
- Symptom directed physical examination, including vital signs and ECOG performance status
- Query patient and all data for adverse events to be assessed using the NCI CTCAE v4.0
- Assessment of Olaparib and Temozolomide drug compliance

- Blood investigations
  - CBC with differential
  - Chemistries
- Patients who do not fulfill criteria for discontinuation of study will remain on study
- Study visits beyond day 21 may occur +/- 5 days of the planned visit date.

5.2.4 Visit 5 (Day 43) and Subsequent Visits every 21 days thereafter

- Review concomitant medications and treatment history since last visit
- Symptom directed physical examination, including vital signs and ECOG performance status
- Query patient and all data for adverse events to be assessed using the NCI CTCAE v4.0
- Assessment for olaparib and temozolomide drug compliance
- Blood investigations
  - CBC with differential
  - Chemistries

Review imaging studies to assess disease status on Day 43, and every 42 days thereafter

- Patients who do not fulfill criteria for discontinuation of study at Day 43 will remain on study and will be seen every 3 weeks thereafter, with repeat imaging studies performed every 6 weeks, according to study calendar.
- Cycle length may be extended to up to 28 days at the discretion of the treating investigator, if for example additional time is needed for bone marrow recovery.

5.2.5 Study Exit

Upon completion and exit from the study, patients will have completed all follow-up visits and evaluations as determined in the schedule of events. Any patient with a treatment-related medical event that requires additional follow-up must continue to be monitored as long as is medically appropriate.

5.2.6 Exit Visit (30 + / - 7 days after last dose)

The following lab studies and procedures should be performed at the exit visit. If the below procedures cannot be done because the study participant is unable or unwilling to return to the study institution, then the followed data should be obtained by telephone call or email to the study participants' local physician and laboratory.

- Review concomitant medications and treatment history since last visit
- Complete physical examination, including vital signs and ECOG performance status
- Query patient and all data for adverse events to be assessed using the NCI CTCAE v4.0
- Blood investigations
  - CBC with differential
  - Chemistries

5.2.7 Patient Discontinuation Prior to Study Completion

Patients who have received olaparib and temozolomide and are unable to complete all study visits will be asked to return for an orderly withdrawal from the study and to complete necessary medical evaluations when appropriate (See Section 5.2.5).

5.3 Olaparib and temozolomide Administration

Olaparib and temozolomide will be administered on days 1-7, every 21 days.

Olaparib tablets will be counted out and dispensed in regular pharmacy plastic prescription bottles or dispensed in original bottles with a child-proof cap and dispensed to patients on Day 1 and every 3 weeks thereafter until the patient completes the study, withdraws from the study or closure of the study.

Temozolomide will be prescribed as up to a 21-day supply (to provide enough temozolomide for up to three cycles of treatment) and renewed as needed during the study. Participants will be weighed on day 1 of each cycle. If the weight has changed by >10% compared to the prior weight used for temozolomide dosing, then temozolomide should be re-prescribed at the dose to reflect the current weight. If the weight has changed by ≥ 5% compared to the prior weight used for temozolomide dosing, then the temozolomide dose may be re-prescribed based on the current weight, at the investigator's discretion. Temozolomide will be dosed at the nearest 5 mg dose interval using the fewest amount of capsules as possible and will be dispensed by the participant's local pharmacy.

Temozolomide should be taken on an empty stomach with approximately 240 mL of water. Participants should wait at least two hours after eating, take their dose, and continue fasting for at least another hour before eating anything. Temozolomide should be taken at bedtime. There is no restriction around food for timing of olaparib dosing. Twice daily doses of olaparib should be taken approximately 12 hours apart, and if dose reductions require once daily dosing, then doses should be taken in the morning unless otherwise instructed. Participants should be instructed to avoid consuming grapefruit juice while enrolled on the study.

Olaparib and temozolomide should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs after the olaparib or temozolomide is swallowed, the dose should not be retaken. 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), 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.

Patients will continue olaparib and temozolomide dosing until objective disease progression (determined per RECIST 1.1) or unacceptable toxicity.

5.4 Laboratory safety assessment

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated.

Coagulation [activated partial thromboblastin time {APTT} and international normalised ratio {INR}] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

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

For the phase 2 portion of the study, subjects with creatinine clearance less than or equal to 50 cc/min should reduce dose of olaparib from 200 mg PO BID days 1-7 to 100 mg PO BID days 1-7.

Urinalysis should be performed at baseline and then only if clinically indicated.

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

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

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

In case a subject shows an AST or ALT ≥ 5 x ULN or total bilirubin ≥ 2xULN please contact the overall study PI, Dr. Anna Farago, for further instructions.

Resting 12-lead ECG

ECGs are required within 28 days prior to starting olaparib and temozolomide administration.

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

Serum or urine pregnancy test

Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential; one at screening within 28 days prior to the start of study treatment, and the other within 7 days of the study prior to commencing treatment. If the screening test falls within 7 days of Day 1, then one pregnancy test will suffice. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

Bone marrow or blood cytogenetic analysis

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

5.5 General Concomitant Medication and Supportive Care Guidelines

Restrictions during the study:

Any medications, with the exceptions noted below, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the eCRF.

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

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

Anticoagulant Therapy: Patients who are taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

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

Antiemetic Therapy: usual antiemetic therapy is allowed as per institutional standard of care.

PCP Prophylaxis: at the investigator’s discretion, PCP prophylaxis may be given if determined to be necessary for prevention of PCP while receiving temozolomide therapy.

Contraception

Females of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception. This should be started from the signing of the informed consent and continue throughout their participation in the study and for at least 3 months after the last dose of olaparib and temozolomide. Male patients and their partners, who are sexually active, must agree to use two highly effective forms of contraception. This should be started from the signing of the informed consent and continue throughout their participation in the study and for 3 months after the last dose of olaparib and temozolomide, if the partner is of child bearing potential.

- Condom with spermicide and one of the following:
- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal ligation plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom+spermicide, provided coils are copper-banded

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon, Norplan)+male condom with spermicide
- Normal and low dose combined oral pills+male condom with spermicide
- Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
- Intravaginal device+male condom with spermicide (eg, EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

5.6 Concomitant medications

CYP3A4 inhibitors

The use of any natural/herbal products or other "alternative therapies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded in the eCRF.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. Olaparib can inhibit CYP3A4 and UGT1A1 in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (e.g. irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

The following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib, and participants who have been taking any of the below drugs will require a one week wash-out period prior to starting olaparib:

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

In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following CYP3A4 inducers should be avoided, and participants who have been taking any of the below drugs will require a three week wash-out period prior to starting olaparib:

- phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (Hypericum perforatum)

Participants who have been taking any of the below drugs will require a five week wash-out period prior to starting olaparib:

- phenobarbitone

After starting day 1 of this study, if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the Principal Investigator (Dr. Anna Farago). A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Palliative radiotherapy

Palliative radiotherapy is permitted on study. If palliative radiation is clinically indicated, it should be performed between cycle days 8 and 21, when patients are not actively taking study medications. If needed, subsequent cycles should be delayed to prevent concurrent radiotherapy and dosing of olaparib and temozolomide. The need for palliative radiotherapy will be taken as clinical indication of insufficient therapeutic benefit and will be counted as disease progression. Stereotactic radiosurgery (or equivalent focal radiation) to asymptomatic brain metastases is allowed. If stereotactic radiosurgery (or equivalent focal radiation) to asymptomatic brain metastases is performed, it should be performed between cycle days 8 and 21, when patients are not actively taking study medications.

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 for bone disease and corticosteroids for the symptomatic control of brain metastases or nausea. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the eCRF

Other Concomitant treatment

Live virus and bacterial vaccines SHOULD NOT be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

5.7 Duration of Olaparib and Temozolomide Administration

Duration of olaparib and temozolomide administration will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, olaparib and temozolomide administration may continue until one of the following criteria applies:

- Disease progression by RECIST 1.1, unless the patient is deriving clinical benefit from treatment as determined by the treating investigator. All such cases must be discussed with the Principal Investigator
- Intercurrent illness that prevents further administration of treatment,

- Participant experiences a DLT (See Section 5) or unacceptable adverse event(s) (See Section 6.3), with the following exception. If the DLT resolves to grade ≤ 1 in ≤ 7 days then the participant may restart study drugs and continue on study with dose modification as per section 6.3 and with the approval of the principal investigator. If the DLT does not resolve with the above specifications, then the participant will undergo an exit study as per section 5.2.6, and will be followed for resolution of any toxicities as per section 5.8
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.
- Participant develops new bone marrow findings consistent with myelodysplastic syndrome/acute myeloid leukemia.

5.8 Duration of Follow Up

Participants will be followed for new adverse events for 30 +/- 7 days after removal from study or until death, whichever occurs first. Participants removed from study for DLT or unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Participants will be followed by telephone or clinic visits every 3 +/- 1 month for survival.

5.9 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.7 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Anna Farago, MD PhD, at (617)-724-4000.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) which is available at http://ctep.cancer.gov/reporting//ctc.html).

In the case of toxicity, appropriate medical treatment should be used (including analgesics, anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

Toxicities of olaparib may include but not limited to the following:

Likely

Fatigue
Nausea
Vomiting
Anemia
Headache
Neutropenia
Lymphopenia
Thrombocytopenia
MCV elevation

Frequent Dyspepsia
Dizziness
Dysgeusia

Rare Pneumonitis
Myelodysplastic syndrome AML

Other side effects (adverse reactions) have been observed in previous studies that include diarrhea, abdominal pain, decreased appetite, constipation, edema, weight loss, tachycardia, thromboembolic events, hyponatremia, but it is not yet known if these were related to olaparib, or if they were unrelated events possibly due to the patient's cancer or other cause. Assessing the full range of side effects of olaparib is an important part of this study.

Toxicities of temozolomide include:
hematological toxicities (leucopenia, lymphopenia, thrombocytopenia, and anemia), renal insufficiency, nausea and vomiting, liver enzyme abnormalities, lethargy, rash, headache, alopecia, constipation, fatigue/malaise, anorexia, hyperglycemia and diarrhea are known toxicities.

Refer to the package insert for additional information on adverse events observed to date. Rats given temozolomide in recent multidose toxicity studies have developed adenocarcinoma of the breast, fibrosarcomas, malignant Schwannomas (a variant of fibrosarcoma), keratoacanthomas and basal cell adenomas. Similar studies conducted in dogs did not reveal any similar findings. The significance of this finding for humans is not known.

Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Patients with known or suspected hypersensitivity to temozolomide should not be treated with temozolomide. There are no data available on the effect or management of temozolomide overdose.

6.2 Toxicity Management

Other than for a DLT observed during the DLT evaluation phase, any toxicity observed during the course of the study may be managed by a dose interruption of both olaparib and temozolomide if deemed appropriate by the Investigator. Treatment must be interrupted if any clinically significant NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of olaparib and temozolomide. Treatment delays will not alter study assessment days.

Repeated dose interruptions are allowed as required, for a maximum of 14 days per interruption if within the DLT monitoring period, or 28 days per interruption if patient is no longer being monitored for DLT. For clinically significant grade 3 or 4 toxicities, olaparib and temozolomide must be interrupted together until the patient recovers completely, reaches baseline, or the toxicity reverts to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.02) grade 1 or less. When the toxicity is appropriately resolved, the patient can resume treatment with both olaparib and temozolomide.. If treatment is held for 14 or fewer days, treatment may restart at the same dose level. If treatment is held for > 14 days, treatment should restart at at least one dose level below the participant's current dose according to the dose level table in section 5. For patients enrolled before July 7, 2017, dose reduction by more than one dose level is acceptable, at the discretion of the investigator. For patients enrolled after July 7, 2017, dose reductions should occur by one dose level at a time, from dose level 3 to dose level 2A to dose level 1 as needed. Dose reductions by more than one dose level per cycle require prior approval from the principal investigator. Dose reductions to lower than dose level 1 should be discussed with the principal investigator. If the event recurs with the same severity following re-challenge with olaparib and temozolomide, treatment should be interrupted again, and on resolution, a further dose reduction made. A maximum of 3 dose reductions will be allowed.

If, on re-starting treatment following 3 dose reductions, the event continues to occur at the same severity, treatment should be permanently discontinued. If the toxicity has not resolved to at least grade 1 during the maximum 28-day period, and/or the patient has already undergone a maximum of 3 dose reductions already, and/or the patient is receiving the lowest dose level of olaparib and temozolomide, then the patient must permanently discontinue treatment with olaparib.

The dose of olaparib or temozolomide may be maintained at the current dose level for grade 3-4 gastrointestinal adverse events as long as it has been maximally managed with appropriate prophylactic measures for at least 7 days. Alternatively, at the Investigator's discretion, the dose level can be reduced. In all cases where the olaparib dose has been interrupted or the patient discontinued due to unusual or unusually severe toxicity considered related to olaparib or temozolomide, the Investigator must contact the Principle Investigator. All dose modifications and interruptions (including any missed doses), and the reasons for the modifications/interruptions are to be recorded in the CRF.

Myeloid growth factors (i.e. GCSF) will not be used in this study. If myeloid growth factors are required, the patient will be removed from the study. If this occurs during the dose-evaluation phase, this will be considered a DLT. If the AE can be managed by transfusions as deemed appropriate by the investigator, olaparib and temozolomide administration may continue without interruption or change in dose.

If any study treatment is interrupted/delayed as outlined above, weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤1 after 4 weeks of dose interruption, the patient should be referred to a hematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard hematological practice regardless of whether or not the patient has been discontinued from taking olaparib and temozolomide.

If a bone marrow analysis is carried out it 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. Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided by the Investigator for documentation on the Patient Safety database. If a bone marrow or blood cytogenetic and flow cytometry is conducted the presence or absence of abnormalities (YES/NO) will be documented for cytogenetics and flow cytometry on the clinical database.

Management of new or worsening pulmonary symptoms: If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib and temozolomide is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib and temozolomide can be restarted, if deemed

appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the study PI (Dr. Anna Farago).

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

Olaparib and temozolomide should be stopped 7 days before surgery and re-started only after wound has healed following recovery. The maximum time allowed for holding both drugs is 28 days.

Olaparib and temozolomide should be stopped 3 days before biopsy and re-started the day after the biopsy if there have been no complications.

Important medical procedures to be followed by the investigator:

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 for single agent administration of olaparib is 300 mg bid (tablet).

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

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

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

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

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

Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

Maternal exposure

If a patient becomes pregnant during the course of the study both olaparib and temozolomide 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) should be followed up and documented even if the patient was withdrawn from the study.

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

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

The same timelines apply when outcome information is available.

Paternal exposure

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

6.3 Dose Modifications/Delays

Patients will temporarily discontinue both olaparib and temozolomide for the following criteria:

Criteria for discontinuation of therapy as listed in Section 5.7 or criteria for DLT as listed in Section 5 are not met AND one of the following criteria are met:

- Grade 4 neutropenia

- Grade 2-3 neutropenia with documented fever or infection
- Platelet count lower than 50 x 10^9/L
- Clinically significant non-hematological toxicity grade 3 or greater, except lymphopenia, nausea, vomiting or diarrhea and fatigue which have not been managed appropriately (e.g. patient has not received anti-emetics) OR clinically insignificant biochemical blood results.
- Aspartate transaminase (AST) or alanine transaminase (ALT) elevations grade 3 or higher for more than 7 days.
- New or worsening pulmonary symptoms or radiological abnormality occurs which are suggestive of pneumonitis
- Any other toxicity that, in the view of the principal investigator, represents a clinically significant hazard to the patient

If treatment is temporarily discontinued for a hematologic toxicity, treatment should be withheld until the toxicity is ≤ grade 1. If treatment is held for 14 or fewer days, treatment may restart at the same dose level. If treatment is held for > 14 days, treatment should restart at at least one dose level below the participant's current dose according to the dose level table in section 5. Dose reduction by more than one dose level is acceptable, at the discretion of the investigator. Dose reductions to lower than dose level 1 should be discussed with the principal investigator. Treatment should restart within a period not longer than 28 days from the planned cycle start. Patient will not make up missed drug doses.

If a patient develops a clinically significant grade 2 non-hematological toxicity, olaparib and temozolomide may be withheld at the discretion of the investigator if it is deemed to be in the best interest of the patient to do so, until the toxicity resolves to ≤ grade 1 or returns to baseline, and treatment may restart at the same dose. Treatment should restart within a period not longer than 28 days. Patient will not make up missed drug doses.

If a patient develops clinically significant grade 3 non-heme toxicity, olaparib and temozolomide must be withheld until the toxicity resolves to ≤ grade 1 or returns to baseline, and treatment may restart at the same dose if it is resumed within 14 days. Treatment should restart within a period not longer than 28 days. Patient will not make up missed drug doses.

When toxicity re-occurs following re-challenge with olaparib and temozolomide, or when dose discontinuation is required for > 14 days due to clinically significant toxicity, the dose should be held until toxicity resolves to ≤ grade 1 or returns to baseline, and treatment may restart at one dose level below the participant's current dose according to the dose level table in section 5. Patients who are on

dose level -3 cannot be dose reduced any further and must be removed from study if a clinically significant toxicity occurs.

A dose reduction can occur at any point the investigator feels that it is at the best interest of the participant. Dose can be re-escalated to a previously administered dose at the permission of the overall study PI if the investigator feels that it is at the best interest of the participant.

Participants should be considered for removal from study if any of the following treatment-related toxicity/ interruption is present:

- Clinically significant grade 4 non-heme toxicity.
- Any toxicity in the opinion of the investigator that precludes further therapy
- Any significant toxicity that occurs while subject is receiving dose level -3.
- Treatment interruption of > 28 days from the planned cycle start date, unless the patient is achieving clinical benefit from protocol treatment as determined by the investigator, and deemed to be in the best interest of patient to continue with protocol therapy. Such cases will be decided upon on a case-by-case basis after discussion with the Principal Investigator.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Olaparib

7.1.1 Description

Drug substance

Chemical Name: 4-[3-(Cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2-H-phthalazin-1-one
Laboratory Codes: AZD2281, KU-0059436; CO-CE 42; PARPi
CAS No.: 763113-22-0
Molecular Formula: C24H23FN4O3
Molecular Weight: 434.47

Physical and chemical properties

Olaparib is an off-white to pale yellow/pale orange crystalline solid, with melting point of 210~211˚C (by density scanning calorimetry [DSC]).

Evidence of chemical structure is provided by 1H- and 13C- nuclear magnetic resonance, mass spectrum, ultra violet and Fourier transform infra red spectra, DSC and X-ray diffraction. Olaparib

is non-chiral. Olaparib is freely soluble in dimethylsulphoxide (DMSO) and 1-methyl-2-pyrrolidinone, sparingly soluble in ethanol and methanol, and only very slightly soluble in water (<0.25 mg/mL).

Presentation

Olaparib is presented for oral administration as round (25 mg) or oval (100 mg) tablets. Olaparib tablets are supplied in induction sealed 32 count bottles with desiccant.

Composition

The tablet cores comprise: olaparib, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. The composition of the tablet film-coating is:
hydroxypropyl methylcellulose (HPMC), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

7.1.2 Labeling

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

Each bottle of olaparib will have an investigational product label permanently affixed to the outside in accordance to institutional practice and government regulations.

7.1.3 Storage and Stability

Olaparib and temozolomide should be kept in a secure place under appropriate storage conditions at room temperature. The product should be stored in the pack provided and used according to the instructions on the label.

7.1.4 Compatibility

Olaparib is administered orally. There are no compatibility issues identified

7.1.5 Handling

Routine handling as per local pharmacy guidelines

7.1.6 Availability

Olaparib is an investigational agent and will be supplied free-of-charge from Astra-Zeneca.

7.1.7 Preparation

No special preparations required

7.1.8 Administration

Subjects will begin dosing at the assigned dose level at study entry. Olaparib and temozolomide will be administered with approximately 240 mL of water, 2 hours after and 1 hour before any meals.

7.1.9 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage or to obtain a copy of the DARF.)

7.1.10 Destruction and Return

At the end of the study, unused supplies of olaparib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.2 Temozolomide

Generic name: Temozolomide

Commercial name: Temodar®

Chemical names: 3,4-Dihydro-3-mthyl-4-oxoimidazo-[5,1-d]-1,2,3,5-tetrazin-4-(3H)-one 8-Carbamoyl-3methylimidazol[5,1-d]1,2,3,5-tetrazin-8-carboxamide

Empirical Formula: C6H6N6O6

Molecular weight: 194.15

Appearance: White to light tan/light pink powder

Melting point: Decomposes at 206ºC

Stability: As a solid temozolomide is thermally stable and does not decompose when exposed to normal light conditions. In solution, temozolomide rapidly hydrolyses in a basic environment. Temozolomide demonstrates improved stability in an acid environment, but hydrolyses when heated. Temozolomide 20mg and 100mg capsules are projected to be stable for 30 months, when stored between 2ºC and 30ºC in amber glass bottles. Temozolomide 5 mg and 250 mg capsules

are projected to be stable for 12 months under the same conditions. The product label recommends storage between 2ºC and 30ºC.

Half life: 1.24 hours at 37ºC in phosphate buffer (0,2M) at pH 7.4

Packaging, dispensing and storage

Temozolomide is available in hard gelatin capsules containing 5, 20, 100, 250 mg. Capsules should be stored between 2ºC and 30ºC and protected from moisture. Capsules are stable at room temperature for at least 2 years. Labeling of the bottles containing the capsules will be done in accordance with the local procedures (as required by law).

Ordering

Temozolomide will be prescribed to each participant via a local pharmacy and billed to the participants' insurance company. Participants should bring temozolomide pill bottles to the clinic for C1D1 administration.

Astra-Zeneca will provide olaparib to the investigational pharmacy at Massachusetts General Hospital. Olaparib will be distributed to Dana Farber Cancer Institute and Beth Israel Deaconess Medical Center via a distributor, Biologics.

All drug orders should be submitted via email to Gayle Ewing (gayle.ewing@astrazeneca.com).

The email should include:

- Title of the ISS: A Phase Ib/II trial of Olaparib and Temozolomide in Adult Patients with Recurrent Small Cell Lung Cancer After Failure Following Prior Chemotherapy
- ISS #: 22810111: Farago
- Formula requested (this study is for tablets only)
- Quantity and Strength

Please allow a minimum of 4 weeks notice to allow enough time for request processing.

Administration

Temozolomide will be taken at bedtime, 2 hours after and 1 hour before any meals. A record of dosing will be kept by the patient for the duration of the trial.

8. CORRELATIVE/SPECIAL STUDIES

If available, up to 10 unstained slides of clinically archived tumor samples will be obtained for DNA/protein analysis.

Subjects will also undergo an optional tumor biopsy performed at pretreatment and within 4-6 weeks of starting olaparib and temozolomide, as long as the biopsy is deemed to be low risk by the investigator. Optional biopsies will be offered during the phase 1 portion of the study only, due to budget limitations. Attempts should be made to obtain at minimum 3 cores, 1 core to be flash frozen on dry ice for RNA analysis, 1 core to be processed to make 10 unstained slides for DNA and protein-based studies, and 1 core to be used clinically to confirm small cell lung cancer histology (sent to surgical pathology). If only 1 core can be obtained, it should be processed to make 10 unstained slides for DNA and protein-based studies. If more than 3 cores are obtained, extra cores will be transported to the MGH Center for Cancer Research at the Charlestown Navy Yard campus.

Tumor samples will be analyzed for MGMT promoter methylation status using a methylation-specific polymerase chain reaction (PCR) assay that is standardized in the MGH molecular pathology laboratory. Tumor samples will also be analyzed for PAR levels at the MGH Center for Cancer Research at the Charlestown Navy Yard Campus using enzyme immunosortbant assays (Liu et al., 2008). Because the scientific assays used to interrogate tumor specimens are constantly evolving, additional tumor samples may be used for research purposes in exploratory studies. These studies may include DNA sequencing (including gene-specific, whole exome, and whole genome sequencing), RNA sequencing (including RT-PCR, Q-PCR, and whole transcriptome sequencing), DNA methylation studies (including CHIP-sequencing), and proteomics assays. Live tissue may also be cultured in vitro and/or implanted into immunodeficient mice to generate xenograft models. Any exploratory research studies will be performed at the MGH Center for Cancer Research at the Charlestown Navy Yard Campus.

9. STUDY CALENDAR

Pre-study laboratory evaluations may be conducted within 28 days prior to start of protocol therapy. Patients will have cycle 1 day 1 labs resulted and reviewed to confirm that they meet lab eligibility before being dosed. . Pre-study laboratory evaluations done within 7 days do not need to be repeated on day 1. Scans must be done within 28 days prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. All assessments must be performed prior to administration of any study medication. All subsequent visits, treatment, procedures and investigations beyond the first visit will be performed within a window of +/- 7 days. Laboratory assessments can be performed locally.

	Pre-Study	**Day 1 (Wk 1)**	**Day 4**	**Day 8 (Wk 2)**	**Day 15 (Wk 3)**	**Day 22 (Wk 4)**	**Day 43 and beyond * (Wk 7 and beyond)**	**Day 4**	**Exit Visit[i]**
Informed Consent **	X								
History	X	X		X	X	X	X		X
Concurrent meds	X	X		X	X	X	X		X
Physical exam (VS and weight)	X	X		X	X	X	X		X
Performance Status	X	X		X	X	X	X		X
CBC w/diff	X	X [c]	X [j]	X	X	X	X	X [j]	X
Serum chemistry [b]	X	X [c]	X [j]	X	X	X	X	X [j]	X
Tumor Biopsy (optional, phase 1 portion only)	X					X[g]			
Coagulation [d]	X					X [h]			
Urinalysis [e]	X								
Pregnancy test	X	X[c]							
Adverse event evaluation				X	X	X	X		X
Drug Compliance				X		X	X		X
Radiologic evaluation	X						X [f]		
ECG	X			X					
Review of Pathology	X								

* +/- 7 day visit window after C1 has been completed

** Reconsent is not required as long as treatment starts within 28 days of original consent.

[a] From Day 43, patients will be seen on day 1 of each cycle, with cycle length 21 days, though cycle length can be extended to up to 28 days at the discretion of the treating investigator. Evaluations as per Day 43.

[b] sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH].

[c] Repeat if screening labs were done more than 7 days prior to Day 1. If screening labs were done more than 7 days prior to Day 1, patients will have cycle 1 day 1 labs resulted and reviewed to confirm that they meet lab eligibility before being dosed.

[d] Coagulation [activated partial thromboblastin time {APTT} and international normalized ratio {INR}] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

[e] Urinalysis should be performed at baseline and then only if clinically indicated.

[f] Radiological evaluations will be performed every 6 weeks of treatment thereafter

[g]. on treatment biopsy can be done anytime between weeks 4 to 6

[h]. PT/INR should be drawn at same time as other week 4 lab tests in preparation for biopsy

[i]. The duration of olaparib and temozolomide administration will be determined as specified in section 5.7. Follow up for survival will be performed by telephone contact or clinic visits every 3 months (+/-1 month) after exit visit until the participant is deceased or lost to follow up.

[j] Subjects with grade ≥2 ALT, AST or total bilirubin level on day 1 of any cycle should have labs (comprehensive metabolic panel, CBC with differential) checked on day 4.

10. MEASUREMENT OF EFFECT

Participants will be assessed by RECIST criteria version 1.1. For the purposes of this study, participants should be evaluated at baseline, after 6 and 12 weeks of olaparib therapy and q6 weeks thereafter.

10.1 Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Eisenhauer et al., 2009). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria version 1.1.

10.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment, and after at least one post-baseline safety follow-up, will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one dose of study medication, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression and die prior to the end of the 21 day DLT measuring period will also be considered evaluable for objective tumor response).

10.1.2 Disease Parameters

Measurable Tumor Burden

A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.

Minimum Size of Measurable Lesions

- ≥ 10 mm in LD and 2X the slice thickness for extranodal lesions
- ≥ 15 mm in short axis diameter (SAD) for nodal lesions
- ≥ 10 mm in LD for clinical lesions (must be measured using electronic calipers)
- chest x-ray cannot be used to measure lesions
- US cannot be used to measure lesions

Lymph Nodes

Lymph nodes are considered pathologically enlarged if > 10 mm in SAD. To be measurable, nodal lesions must be ≥ 15 mm in SAD. Nodal lesions with SAD > 10 mm and < 15 mm are non-measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.

Bone lesions

A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, PET, or plain films are non-measurable.

Lesions with Prior Local Treatment

Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy. Conditions should be defined in study protocols.

Too Small to Measure

If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and within 28 days prior to cycle 1 day 1.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation by CT or MRI is required.

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

Chest x-ray. Lesions on chest x-ray will not be acceptable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). US should not be used to measure tumor lesions.

10.1.4 Response Criteria: RECIST 1.1

10.1.4.1 Evaluation of Target Lesions

Complete Response (CR): CR requires the disappearance of all extranodal lesions, the regression of all nodal lesions to < 10 mm on short axis dimension.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Progressive Disease (PD): PD is assessed if the sum of the diameters has increased by ≥ 20% and ≥ 5 mm from nadir (including baseline if it is the smallest sum).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing, an overall assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

10.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions.

Progressive Disease (PD)

Patients with measurable disease: for “unequivocal progression” based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR).

Patients without measurable disease: for “unequivocal progression” of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time by review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable or progressive disease status.

10.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	
CR	NonCR/Non-PD	No	PR	
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.1.5 Progression-Free Survival

Progression Free Survival (PFS) is defined as the duration of time from date of registration to date of disease progression (according to RECIST 1.1 criteria) or death due to any cause, whichever comes first. Subjects who are alive without disease progression will be censored at the last disease assessment date.

10.1.6 Overall survival

Time from date of study registration to death due to any cause.

10.1.7 Response Review

As this is an investigator initiated research trial, a central review of the radiology assessments is not planned.

10.2 Antitumor Effect – Hematologic Tumors

Not Applicable

10.3 Other Response Parameters

Not Applicable

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from signing of consent, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event or related to a study procedures and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2 Definitions

11.2.1 Adverse Event (AE)

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

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

11.2.2 Serious adverse event (SAE)

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

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

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

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- treatment planned before signing informed consent for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care
- Abnormal lab values that do not require medical intervention to return to baseline value

11.2.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.

11.2.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.2.3.2. Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.3 Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs).

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE v4.0 grade and the maximum CTC grade attained
- Whether the AE is serious or not

- Investigator causality rating against the Investigational Product (yes or no) comparator/combination drug (yes/no)
- Action taken with regard to investigational product/comparator/combination agent
- Outcome.

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 11.2.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

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

If deterioration in a 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 (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a 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.

NB. Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs.

Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of *new, 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/SAE during the study.

New cancers

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

Lack of efficacy

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

Deaths

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

1. Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.
2. Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours**. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.
3. 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.

11.4 Reporting Adverse Events

The Sponsor-Investigator must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

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

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

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

**** Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229***

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

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

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

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

11.5 Sponsor Notification by Investigator

11.5.1 Serious Adverse Event Reporting Requirements

All events meeting the criteria for Serious Adverse Event (See Section 11.2.2) that occur after time of consent, the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported as serious adverse events.

The participating investigator must report each serious adverse event, regardless attribution, to the Principal Investigator (Dr. Anna Farago) within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone and email to:

Principal Investigator:
Anna Farago, MD Tel: 617-724-4000 Email: afarago@partners.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.5.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events will be reported to the Principal Investigator (Dr. Anna Farago) on the toxicity Case Report Forms.

11.6 Institutional Review Board (IRB) Notification by Investigator

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator (Dr. Anna Farago) and to the IRB according to the local IRB's policies and procedures in reporting adverse events.

11.7 Food and Drug Administration (FDA) Notification by Sponsor-Investigator

The Sponsor-Investigator will report to the FDA any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.8 NIH Office of Biotechnology Activities (OBA) Notification by Investigator

Not applicable

11.9 Institutional Biosafety Committee (IBC) Notification by Investigator

Not applicable

11.10 Hospital Risk Management Notification by Investigator

The participating investigator will report to the Principal Investigator (or Protocol Chair) and to local Risk Management any subject safety reports or sentinel events that require reporting according to institutional policy.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with OnCore
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet approximately quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6) www.fda.gov/cder/guidance/iche6.htm
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Institutional research policies and procedures www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

Not applicable

13.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not applicable

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

The study is a single arm, open label, phase I/II study.

The primary objective of the phase I portion is to determine the MTD and RP2D of olaparib and temozolomide in patients with recurrent SCLC. Its corresponding endpoint is the presence of a DLT as defined in Section 5.

The primary endpoint of the phase II portion is response rate to olaparib and temozolomide in patients with recurrent SCLC as defined in Section 10.1.

14.2 Sample Size/ Accrual Rate

<u>Phase I portion:</u>

This study aims to find the MTD of olaparib when given with temozolomide and to characterize the most frequent adverse events and the DLTs.

Dose-limiting toxicities will be evaluated on Cycle 2 day 1 and will include all adverse events experienced between days 1-21. Patients terminated for reasons other than a defined DLT will be replaced.

Experience from at least six evaluable patients will be used to determine the MTD.

The algorithm-based design of the dose escalation part of the study is specified because of its practical simplicity and not because of power considerations. A dose level will be determined intolerable if any of the following scenarios of DLT occurrence are observed: 2 or 3 of the first 3 patients experience a DLT, or one of the first 3 patients and one or more of the next 3 patients experience a DLT.

Given that the study is at a specific cohort, the probabilities of declaring that dose level intolerable, given various true occurrence rates for DLTs, are presented in Table 4. For example, given a true occurrence rate of 15%, the probability of declaring that dose level intolerable is 18.62%.

Table 4. Probability of Declaring a Dose Level Tolerable or Intolerable at Various DLT True Occurrence Rates

Declare cohort:	**True Occurrence Rate of DLTs**							
	0.10	0.15	0.20	0.25	0.30	0.40	0.50	0.60
Intolerable	0.09	0.19	0.29	0.40	0.51	0.69	0.83	0.92
Tolerable	0.91	0.81	0.71	0.60	0.49	0.31	0.17	0.08

We anticipate that up to 15 evaluable patients will be enrolled in the phase I portion of this study. The design of the study enables up to 24 evaluable patients in the phase I portion, though enrollment of > 15 patients in the phase I portion is highly unlikely. Once the RP2D is determined, an additional 3 or 14 subjects will be enrolled to determine efficacy and to further determine safety and tolerability, as described below.

Doses of olaparib and temozolomide will not exceed the dose levels defined in Table 2. If an MTD is not determined after patients enrolled to dose level 4 have completed the DLT evaluation window, then the RP2D will be determined by the principal investigator, with approval from AstraZeneca, based on the safety data available from the phase I portion of the study.

<u>Phase II portion:</u>

For the phase II portion of the study, the study aims to observe the ORR to olaparib and TMZ in patients with relapsed SCLC. A Simon's two-stage optimal design will be used to allow early termination of the protocol due to lack of efficacy. Evaluable patients, defined as those who complete the first restaging scan, will be included in the analysis. Any patients who do not complete the first restaging scan will be replaced. After the first 9 evaluable patients treated at the RP2D are

evaluated for response, accrual will be terminated if <2 partial or complete best overall responses are observed. If ≥2 partial or complete best overall responses are observed, the protocol will proceed to the second stage with enrolling an additional 11 evaluable patients for an accrual of 20 evaluable patients. After the first 20 evaluable patients treated at the RP2D are evaluated for response, accrual will be terminated if <4 partial or complete best overall responses are observed. If ≥4 partial or complete best overall responses are observed, the protocol will proceed to the second stage with enrolling an additional 20 evaluable patients for a total accrual of 40 evaluable patients. If the total number of responders were at least 6 patients, the efficacy will be considered promising. The two-stage design provides 89% power to determine that the RP2D combination of olaparib and TMZ is truly associated with a 30% overall response rate. If the combination were actually inactive with an underlying response rate of only 10% or less, the protocol design has 87% probability of early termination at the first stage and 9% overall probability of erroneously declaring efficacy.

14.3 Stratification Factors

There are no planned patient stratification factors.

14.4 Analysis of Secondary Endpoints

Phase I portion:

The secondary endpoints are assessment of safety and variations in MGMT promoter methylation status and PAR levels in tumor biopsy samples obtained before and during treatment.

Safety will be assessed using CTCAE version 4.0 criteria. Toxicity rates will be estimated based on assessment of the patients in cycles 1 and 2, and will be reported in table format. Toxicity rates (grade 3 or 4 SAE) will be listed in table format. The estimation of toxicity rates will be based on the 9 or 20 participants treated at the RP2D. Toxicity rates can then be estimated within plus or minus the 90% confidence interval. Summary statistics will be provided as appropriate and the relationship between different parameters will be assessed.

MGMT promoter methylation status (positive or negative) will be assessed as positive or negative on pre-treatment and on-treatment biopsies using standard laboratory techniques performed in the MGH pathology department. MGMT methylation status before treatment will be correlated to response rate using a one-sided Fisher's exact test. We hypothesize that cases with MGMT promoter methylation will have a higher response rate than cases without MGMT promoter methylation.

PAR levels will be measured before and during treatment and levels will be assessed in the MGH Cancer Center laboratory in Charlestown MA and will be reported as continuous variables using a standard enzyme-linked immunoabsorbant assay (Liu et al., 2008). PAR levels will be directly compared for each patient to determine how levels change in response to treatment using a one-sided t test. We hypothesize that PAR levels will be lower on-treatment than pre-treatment for each patient.

Phase II portion:

The secondary endpoints are assessment of safety, PFS, and OS.

Safety will be assessed using CTCAE version 4.0 criteria. Toxicity rates will be estimated based on assessment of the patients in cycles 1 and 2, and will be reported in table format. Toxicity rates (grade 3 or 4 SAE) will be listed in table format. The estimation of toxicity rates will be based on the 9 or 20 participants treated at the RP2D. Toxicity rates can then be estimated within plus or minus the 90% confidence interval. Summary statistics will be provided as appropriate and the relationship between different parameters will be assessed.

Progression Free Survival (PFS) is defined as the duration of time from date of registration to date of disease progression (according to RECIST 1.1 criteria) or death due to any cause, whichever comes first. The assessment will occur 1 year after treatment day 1 of the final patient enrolled or once every patient enrolled on study has died, whichever comes first. Subjects who are alive without disease progression will be censored at the last disease assessment date. PFS will be estimated using Kaplan Meier methods.

Overall Survival (OS) is defined as the duration of time from date of registration to date of death. The assessment will occur 1 year after treatment day 1 of the final patient enrolled or once every patient enrolled on study has died, whichever comes first. Subjects who are alive without disease progression will be censored at the last disease assessment date. Subjects who are alive will be censored at the date of their last follow-up. OS will be estimated using Kaplan Meier methods.

14.5 Reporting and Exclusions

14.5.1 Evaluation of toxicity

In both the phase I and phase II portions of the study, all participants who receive at least one dose of study medication, and after at least one post-baseline safety follow-up, will be evaluable for toxicity from the time of their first treatment.

14.5.2 Evaluation of response

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). By arbitrary convention, category 8 usually designates the "unknown" status of any type of data in a clinical database.

All of the participants who met the eligibility criteria (with the possible exception of those who received no study medication) and who were treated at the RP2D should be included in the main analysis of the response rate. Participants in response categories 4-7 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

15. PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that is reviewed by Astra Zeneca and meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of data collection.

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17. APPENDICES

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.