

DF/HCC Protocol #: 20-086

TITLE: Phase II trial of olaparib in combination with ceralasertib in patients with recurrent osteosarcoma

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NCT Number: NCT04417062

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Agent Supply: AstraZeneca

IND #: 147750

IND Sponsor: [REDACTED]

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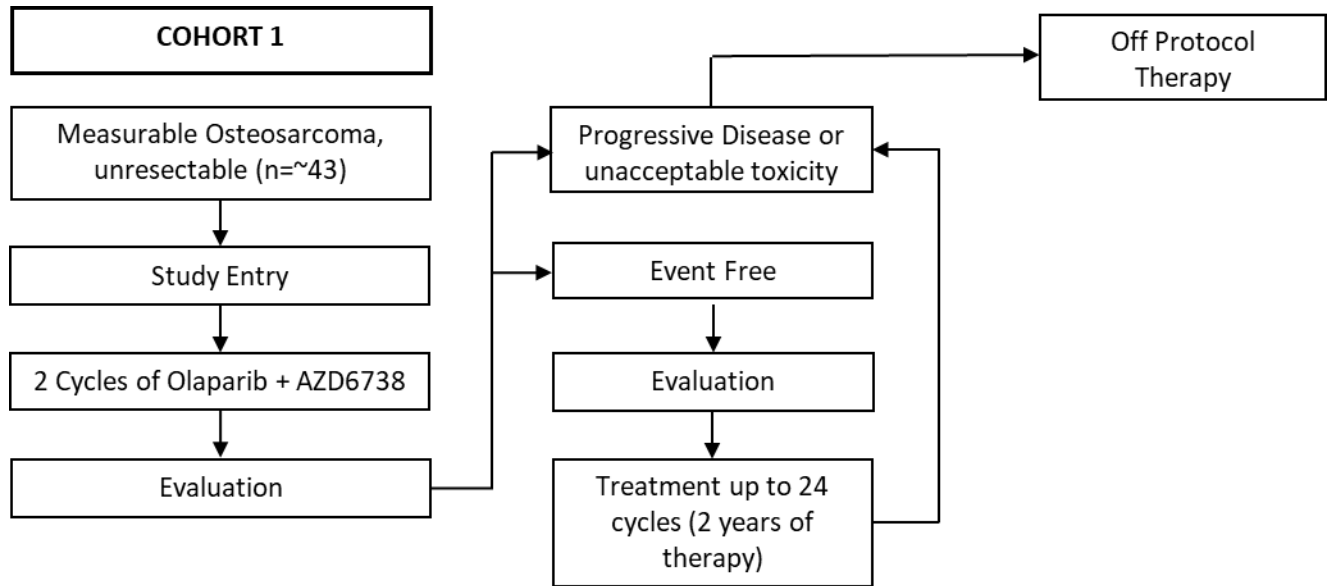
0. ABSTRACT AND SCHEMA

Osteosarcoma is the most common bone tumor of children, adolescents, and young adults (AYA) and the fifth most common pediatric cancer overall. In contrast to other pediatric cancers, there have been no significant improvement in osteosarcoma outcomes in the past 30 years and no novel therapies have been identified to be active in this disease. Recurrence typically occurs as pulmonary metastases and in this clinical setting, the standard of care is resection of all nodules, if feasible. Beyond resection there is no standard of care therapy for patients who develop recurrent osteosarcoma and outcomes are dismal with an overall survival of 20%. Thus, identification of new therapies active in osteosarcoma is a high priority of the research community and will require innovative trials of molecularly targeted therapies, novel preclinical approaches and biomarker discovery. The most significant advances in treatment for other cancers in the past decade have occurred through the use of precision oncology approaches, where molecularly targeted therapies are developed and utilized in cancers driven by specific genomic biomarkers predicting response. This precision oncology strategy has not yet been employed in Phase 2 trials in recurrent osteosarcoma.

Osteosarcoma is characterized by massive genomic alterations including somatic copy number changes and structural rearrangements.¹ These genomic alterations are heterogeneous between patients. Some of these genomic alterations may sensitize osteosarcomas to treatment with PARP and ATR inhibitors.^{2,3} Olaparib is an orally available and potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP). Ceralasertib is an orally available inhibitor of the serine/threonine protein kinase Ataxia Telangiectasia and Rad3 Related (ATR), a member of the phosphoinositide 3-kinase related kinase family.

This is a single arm, phase 2, open-label clinical trial to evaluate the clinical activity of olaparib in combination with ceralasertib in 2 cohorts of patients aged 12-40 with recurrent osteosarcoma. Enrollment will be restricted to patients older than 12 years of age and initially the adult maximum tolerated dose for the combination as determined by the phase I study (NCT 022646780) was utilized (olaparib at a dose of 300mg orally twice a day (BID) on days 1-28 and ceralasertib at a dose of 160 mg orally once a day on days 1-14 of a 28-day cycle). After additional efficacy and pharmacokinetic (pK) data was available, as of protocol v4, the dose was amended to a different tolerable dose from the phase 1 study (NCT02264678). As of v4 of the protocol, participants will receive olaparib at a dose of 150mg orally twice a day (BID) on days 1-28 and ceralasertib will be given at a dose of 80 mg orally twice a day on days 1-14 of a 28-day cycle. Patients can remain on treatment for up to 2 years if they have not progressed. In patients with unresectable disease (Cohort 1), the primary objective will be the proportion of patients event-free at 4-months. This will be compared to a benchmark selected based on the historical experience of 96 patients enrolled on phase 2 trials conducted by the Children's Oncology Group (COG) where the proportion of patients event-free at 4 months is 12% {95% CI: 6.0%-19%}. In patients with resectable disease limited to the lungs (Cohort 2), the primary endpoint will be the submission of paired pre- and post-treatment tumor samples for correlative studies.

EXPERIMENTAL DESIGN SCHEMA



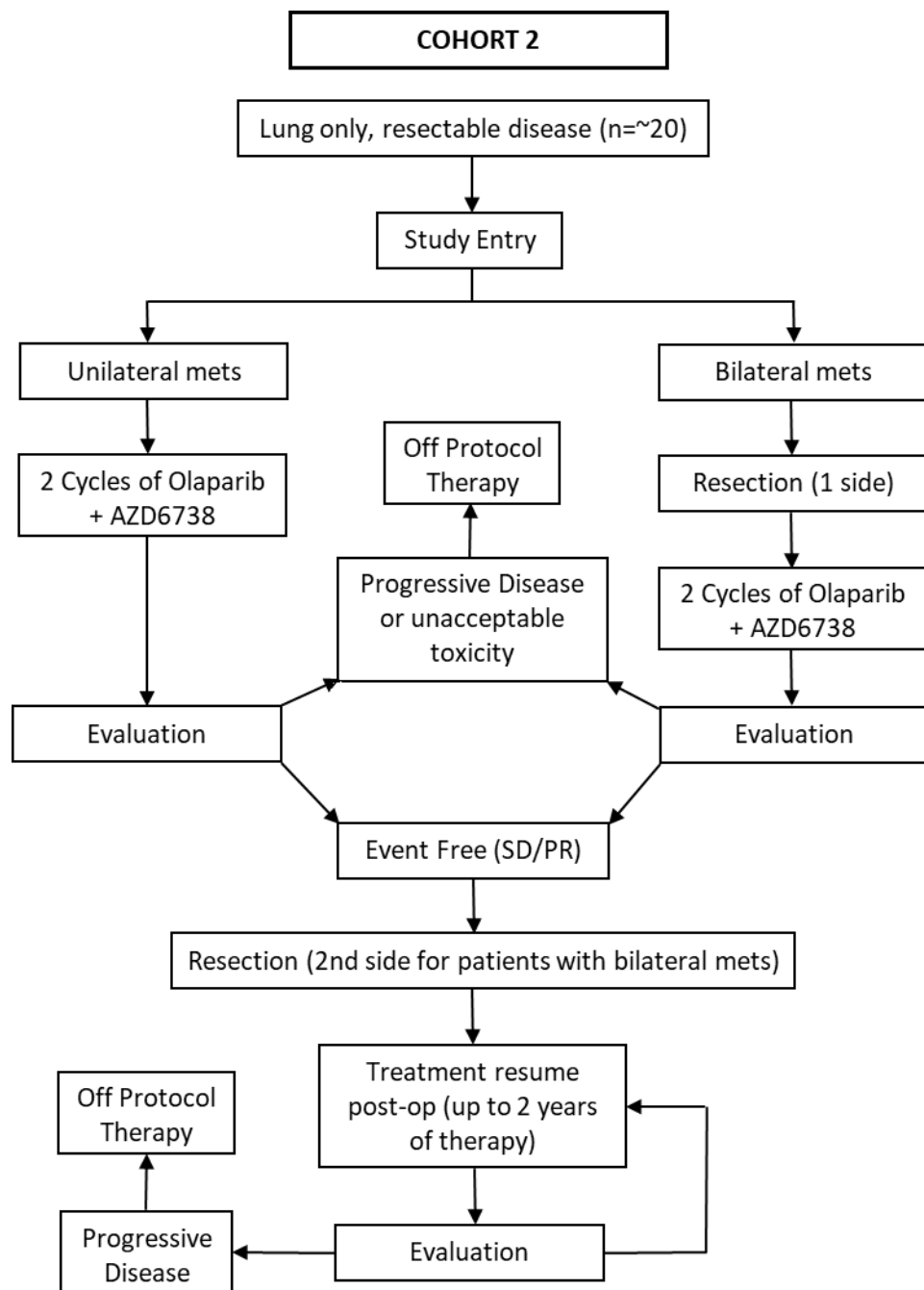


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1. OBJECTIVES

Primary Objective

1. Cohort 1: To determine whether olaparib in combination with ceralasertib improves the 4-month event-free rate in those with recurrent measurable osteosarcoma as compared to a benchmark based on historical COG experience.
1. Cohort 2: To estimate the proportion of patients who have paired pre- and post-treatment tumor samples submitted for correlative studies.

Secondary Objective

1. To evaluate the objective response rate in subjects with relapsed osteosarcoma who receive olaparib in combination with ceralasertib separately for Cohorts 1 and 2.
2. To evaluate the event-free survival (EFS) and overall survival (OS) rate in subjects in treated with olaparib in combination with ceralasertib separately for Cohorts 1 and 2.
3. Cohort 2 only: To describe the 12-month event-free rate in patients who receive olaparib in combination with ceralasertib.
4. To evaluate the safety and tolerability of olaparib given in combination with ceralasertib in patients with recurrent osteosarcoma.

Exploratory Objectives

1. To describe the relationship between gene alterations in the DNA damage response pathway and other biomarkers of DNA damage response, with objective response of olaparib in combination with ceralasertib in recurrent osteosarcoma. If deemed necessary, the relationship between ceralasertib PK and relevant selected biomarker(s) will be assessed.
2. To evaluate a quantitative circulating tumor DNA assay as a surrogate marker for objective response.

1.1 Study Design

This is a single arm, multi-center phase 2, open-label clinical trial to evaluate the clinical activity of olaparib in combination with ceralasertib in 2 cohorts of patients aged 12 to 40 years with recurrent osteosarcoma. Patients with unresectable disease will be enrolled into Cohort 1 and patients with resectable disease which is limited only to the lung parenchyma will be enrolled into Cohort 2. The adult maximum tolerated dose for the combination will be utilized. As of v4 of the protocol, participants in both cohorts will receive olaparib at a dose of 150mg orally BID on days 1-28 and ceralasertib will be given at a dose of 80 mg orally twice a day on days 1-14 in 28-day cycles. Patients can remain on treatment for up to 2 years if disease progression has not occurred.

For Cohort 1, the primary objective in this trial is to evaluate the efficacy of olaparib in combination with ceralasertib in improving the 4-month event-free rate of patients with recurrent osteosarcoma as compared to a benchmark selected based on historical COG experience. The endpoint of event-free status was chosen in contrast to tumor shrinkage due to the fact that the tumor stroma for osteosarcoma consists of a calcified matrix, and radiologic tumor shrinkage does not always correlate with histologic response. Further, a robust baseline has been established for the expected 4-month event-free rate in recurrent osteosarcoma. Baseline evaluations will be obtained prior to initiating study treatment. Disease assessments will occur every 8 weeks. The primary endpoint for the primary objective for Cohort 2 is the submission of paired pre- and post-treatment tumor samples for correlative studies. Safety and tolerability will be evaluated and descriptively summarized.

For Cohorts 1 and 2 key secondary objectives are to evaluate the objective response rate (assessed per

Response Criteria Evaluation Criteria in Solid Tumors (RECIST), version 1.1), EFS rate, and overall survival rate. For Cohort 2, we will also assess the event-free rate at ~12 months in patients with completely resected recurrent osteosarcoma confined to the lung parenchyma. This will be descriptively compared to an historical COG experience. As the first study of ceralasertib in combination with olaparib including patients between 12 and 18 years of age, secondary objectives also include assessing the safety and tolerability of the combination. Additional exploratory objectives are to assess alterations in the DDR pathway and functional biomarkers of DDR with clinical response and to evaluate a quantitative circulating tumor DNA assay as a surrogate marker for response. If deemed necessary, the relationship between ceralasertib PK and any relevant selected biomarker(s) will be assessed.

Sample size and study duration

Total accrual: Up to approximately 63 patients (43 Cohort 1, 20 Cohort 2)

Accrual goal: 34 evaluable patients Cohort 1 patients (participants who are inevaluable will be replaced).

Evaluability for Cohort 1: To be evaluable to address the study's primary objective, i.e., to be included in the two-stage design, a Cohort 1 patient must be eligible and have received at least one dose of protocol therapy including both olaparib and ceralasertib at the dose level instituted with protocol version 4. Participants who enrolled on the trial, but do not received one dose of both olaparib and ceralasertib or who received the initial dose level (prior to protocol version 4) will be deemed inevaluable and will be replaced in the enrollment count of Cohort 1 patients required to address the study's primary objective.

2. BACKGROUND

2.1 Study Disease

Osteosarcoma is the most common bone tumor of children, adolescents, and young adults (AYA) and the fifth most common pediatric cancer overall. There are approximately 450 new cases diagnosed each year in the United States in children and young adults less than 25 years old. The majority of cases occur in the long bones around the knee, with the next most common site being the shoulder. Treatment consists of chemotherapy (cisplatin, doxorubicin, methotrexate and, in some cases, ifosfamide and etoposide) and surgical resection. Metastases, which are present in approximately 20% of patients at diagnosis, most often occur in the lung and standard of care is to perform resection of all lesions, if possible. While the 5-year overall survival of patients with non-metastatic disease is 65-70%, those patients with metastatic disease have a significantly poorer survival of approximately 30%. In contrast to other pediatric cancers, there have been no significant improvement in osteosarcoma outcomes in the past 30 years and no novel therapies have been identified to be active in this disease. Recurrence typically occurs as pulmonary metastasis and in this clinical setting, the standard of care is resection of all nodules, if feasible. The approach to surgical removal of metastatic pulmonary nodules can vary according to surgeon's preference with some performing thoracotomy and some performing thoracoscopy. If there is radiographic evidence of metastases in both lungs, it is most common for metastatic pulmonary nodules to be resected with sequential or stages thoracotomies in which one side is resected and then the other and often systemic treatment is given between surgeries. This is because the recovery from a staged approach is easier. Beyond resection there is no standard of care therapy for patients who develop recurrent osteosarcoma and outcomes are dismal with an overall survival of 20%. Thus, identification of new therapies active in osteosarcoma is a high priority of the research community and can be achieved, in part by conducting phase 2 trials of novel agents in children with recurrent osteosarcoma. If novel agents are found to be active, there is a high likelihood they would be promoted for further study in newly diagnosed patients.⁴ Osteosarcoma is unique in that the tumor stroma consists of a calcified matrix that persists even with significant tumor necrosis. Because of this, objective response rate is not a good surrogate marker for progression free or overall survival.^{5,6} Therefore, we have developed a trial design with osteosarcoma

specific endpoints that has been published in the Journal of Clinical Oncology.⁷ This design accounts for the 2 cohorts of recurrent OS patients typically encountered in clinical practice; those with unresectable, measurable disease (per RECIST v1.1) and those with resectable metastases limited to the lung parenchyma. In patients with unresectable disease, we utilize a an endpoint of event-free status at 4 months. This is compared to a benchmark selected based on the historical experience of 96 patients enrolled on phase 2 trials conducted by the Children's Oncology Group (COG) where the event-free rate at 4 months is 12% {95% CI: 6.0%-19%}. Similarly, in patients with resectable disease limited to pulmonary parenchyma, 12-month event-free rate is compared to a benchmark selected from a historical population. This trial design has been utilized in four COG phase 2 clinical trials approved by the group's scientific council and CTEP (Cancer Therapy Evaluation Program). The trial design has been accepted as an approach for identifying novel agents to be promoted for further study in osteosarcoma by the international community of sarcoma investigators as evidenced by 2 poster presentations of phase 2 trials conducted in Europe and Asia presented at the ASCO annual meeting in 2018, utilizing this or a similar (PFS at 4-months) endpoint.^{8,9} Finally, accrual to phase 2 trials with this design is brisk.¹⁰

Osteosarcoma is characterized by massive genomic alterations including somatic copy number changes and structural rearrangements.¹ These genomic alterations are heterogeneous between patients. Some of these genomic alterations may sensitize osteosarcomas to treatment with DDR inhibitors. For example, some osteosarcomas have a unique mutational signature similar to that seen in BRCA1 deficient cancer and response of osteosarcoma cell lines to PARP inhibitors is correlated with the presence of mutations that alter ability of cells to engage the homologous recombination DNA repair (HR) pathway.^{2,3} Similarly, ATRX, a protein involved in the alternative lengthening of telomeres (ALT), is frequently inactivated by deletion or structural rearrangement in osteosarcoma. Loss of ATRX and resultant defects in the ALT pathway may sensitize tumor cells to another class of DDR inhibitors, the ATR inhibitors and osteosarcoma cell lines have been shown to be sensitive to ATR inhibitors.¹¹

2.2 Study Treatment

2.2.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent inhibitor of Polyadenosine 5'diphosphoribose (PARP) developed as a monotherapy as well as for combination with chemotherapy, ionizing radiation and other anti-cancer agents including novel agents and immunotherapy.

Investigators should be familiar with the current Olaparib Investigator's Brochure (IB).

2.2.1.1 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the Olaparib IB.

2.2.1.2 Toxicology and safety pharmacology summary

The toxicology and safety pharmacology are fully described in the current version of the Olaparib IB.

2.2.1.3 Clinical Experience with olaparib

Clinical experience with Olaparib is fully described in the current version of the Olaparib IB. Investigators should be familiar with the current Olaparib Investigator Brochure (IB). Data on the safety and tolerability of olaparib in humans is presented in the Olaparib IB (Sections 5.2 and 5.4). The key

findings are summarized below:

- [REDACTED]
- The olaparib capsule formulation was registered for use in the EU and US in December 2014 for ovarian cancer. The olaparib tablet formulation is registered for use in the US, EU and Japan for second-line ovarian cancer, germline BRCA mutant (gBRCAm) breast cancer and BRCA mutant (BRCAm) first-line ovarian cancer. In China, the tablet formulation is registered for use as maintenance treatment following response to platinum-based chemotherapy in patients with platinum sensitive recurrent ovarian cancer and as first-line maintenance in BRCAm advanced ovarian cancer patients. [REDACTED]
- The recommended olaparib monotherapy capsule dose is 400 mg twice daily. The recommended olaparib monotherapy tablet dose is 300 mg twice daily.
- Data from Phase I dose escalation studies of olaparib in combination with various chemotherapy agents indicated an increase in bone marrow toxicity (anaemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. However, tolerable regimens combining olaparib with paclitaxel, attenuated dosed liposomal doxorubicin and attenuated dosed carboplatin/paclitaxel have been established, supporting studies in the combination setting.
- [REDACTED]
- [REDACTED]
- Toxicities considered to be associated with administration of olaparib include haematological effects (anaemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), decreased appetite, nausea and vomiting, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis, cough and dyspnoea (see Olaparib IB Section 5.4).

- Cases of pneumonitis, myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) and new primary malignancies have been reported. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are AEs of special interest for olaparib and are being kept under close pharmacosurveillance.
- Olaparib is currently being tested in combination with irinotecan as part of AcSé-ESMART study (European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors Children, ITCC-057), in adolescents and young adults with refractory or recurrent malignancies. Preliminary activity has been observed in patients with neuroblastoma, osteosarcoma and pinealoblastoma. The Phase 2 expansion in ewing sarcoma and other tumors with HR alteration is ongoing and was presented at the 2019 International Society of Pediatric Oncology (SIOP) Annual Meeting.

2.2.2 Ceralasertib

Ceralasertib (AZD6738) is an orally available potent and selective inhibitor of the serine/threonine protein kinase Ataxia Telangiectasia and Rad3 Related (ATR), a member of the phosphoinositide 3-kinase related kinase (PIKK) family.¹² ATR is a serine/threonine kinase that has a role in cell cycle checkpoint regulation as well as DNA repair in response to DNA damage or replication in mammalian cells.¹³ Ceralasertib has the potential to provide benefit as a monotherapy or in combination with DNA damaging agents, including PARP inhibitors, in patients with both hematological and solid malignancies.

Investigators should be familiar with the current ceralasertib Investigator Brochure (IB). Ceralasertib is an orally dosed selective and potent inhibitor of Ataxia Telangiectasia and Rad3 Related (ATR) kinase with good selectivity against other Pi3 kinase family members. ATR is a serine/threonine protein kinase and member of the phosphatidylinositol 3-kinase related kinase (PIKK) family. During normal replication, ATR is recruited at stalled replication forks which can progress to double strand breaks if left unrepaired. ATR is also recruited to single strand DNA coated with Replication Protein A (RPA) following single strand DNA damage or the resection of double strand breaks. Recruitment and activation of ATR leads to cell cycle arrest in the S phase while the DNA is repaired and the stalled replication fork resolved, or nuclear fragmentation and entry into programmed cell death (apoptosis). In the clinic, ATR inhibitors are expected to cause growth inhibition in tumor cells dependent upon ATR for DNA repair e.g. ATM-deficient tumors. In addition to monotherapy activity, ATR inhibitors are also predicted to potentiate the activity of cytotoxic DNA damaging agents and radiotherapy (through inhibition of ATR-dependent DNA repair processes) when used in combination. While significant enhancement of anti-tumor activity may be achieved, data with ceralasertib suggest the potential need to reduce the ATR inhibitor dose and intensity (relative to monotherapy dose) and introduce dosing breaks to allow normal tissue recovery when used in combination with systemic DNA damaging chemotherapy agents, in order to maintain tolerable therapeutic margins. There is also a rationale for combining with anti-PD1/PD-L1 agents as ATR inhibition may stimulate the production of tumor neo-antigens and directly affect the tumor immune microenvironment. The mechanism of action of ceralasertib suggests the potential to combine it with a number of anti-cancer treatments, resulting in either synergistic or additive activity.

2.2.2.1 Pre-clinical experience

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

2.2.2.2 Toxicology and safety pharmacology summary

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

2.2.2.3 Clinical experience with ceralasertib as monotherapy and in combination with Olaparib

Clinical experience with ceralasertib is fully described in the current version of the ceralasertib Investigator's Brochure. Sections 5.2.3 and 5.2.5 summarize the safety data for ceralasertib monotherapy and ceralasertib plus olaparib, respectively. There are no data of ceralasertib monotherapy or in combination with olaparib in adolescents under the age of 18 year.

2.2.2.4 Emerging Safety Data

This section summarises the safety data for the ongoing AstraZeneca sponsored, open-label, Phase I /II clinical studies. This summary represents unclean data. Please see the latest edition of the IB, section 5.4.

This section describes the emerging safety profile with regard to those AEs considered as identified risks for ceralasertib either when used as monotherapy or as part of combination therapy in the ongoing clinical programme, based on toxicology data and the safety profile of the product.

The safety profile of ceralasertib either as monotherapy or in combination with olaparib is consistent with preclinical findings and/or the safety profile of the combination agent.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

[REDACTED]

[illegible]

Age Group	Percentage
18-24	35%
25-34	30%
35-44	25%
45-54	20%
55-64	15%
65-74	10%
75-84	8%
85+	5%

2.2.3 Summary of Risks

This section summarises the safety data for the ongoing AstraZeneca sponsored, open-label, Phase I/II clinical studies (unless otherwise specified). This

represents unclean data. Additional pooled data are provided in ceralasertib IB (Section 5.2 of the IB). The following have been recognised as potential risks for ceralasertib in the ongoing clinical programme based on toxicology data and the safety profile of the product:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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2.2.4 Combination of olaparib and ceralasertib

Preclinical efficacy studies of olaparib and ceralasertib in adult malignancies.

In combination with olaparib, ceralasertib displays synergistic activity by inhibiting olaparib induced and ATR-dependent DNA damage repair mechanisms.¹⁴⁻¹⁷ Specifically, in breast and ovarian cancer cell lines resistant to olaparib, combination therapy with olaparib and ATR inhibitors re-initiates degradation of stalled replication forks. Clinical experience with the combination of olaparib and ceralasertib.

Clinical experience with ceralasertib in combination with olaparib is fully described in the current version the ceralasertib IB, and in protocol sections 2.2.2.4 and 2.2.3.

2.3 Rationale

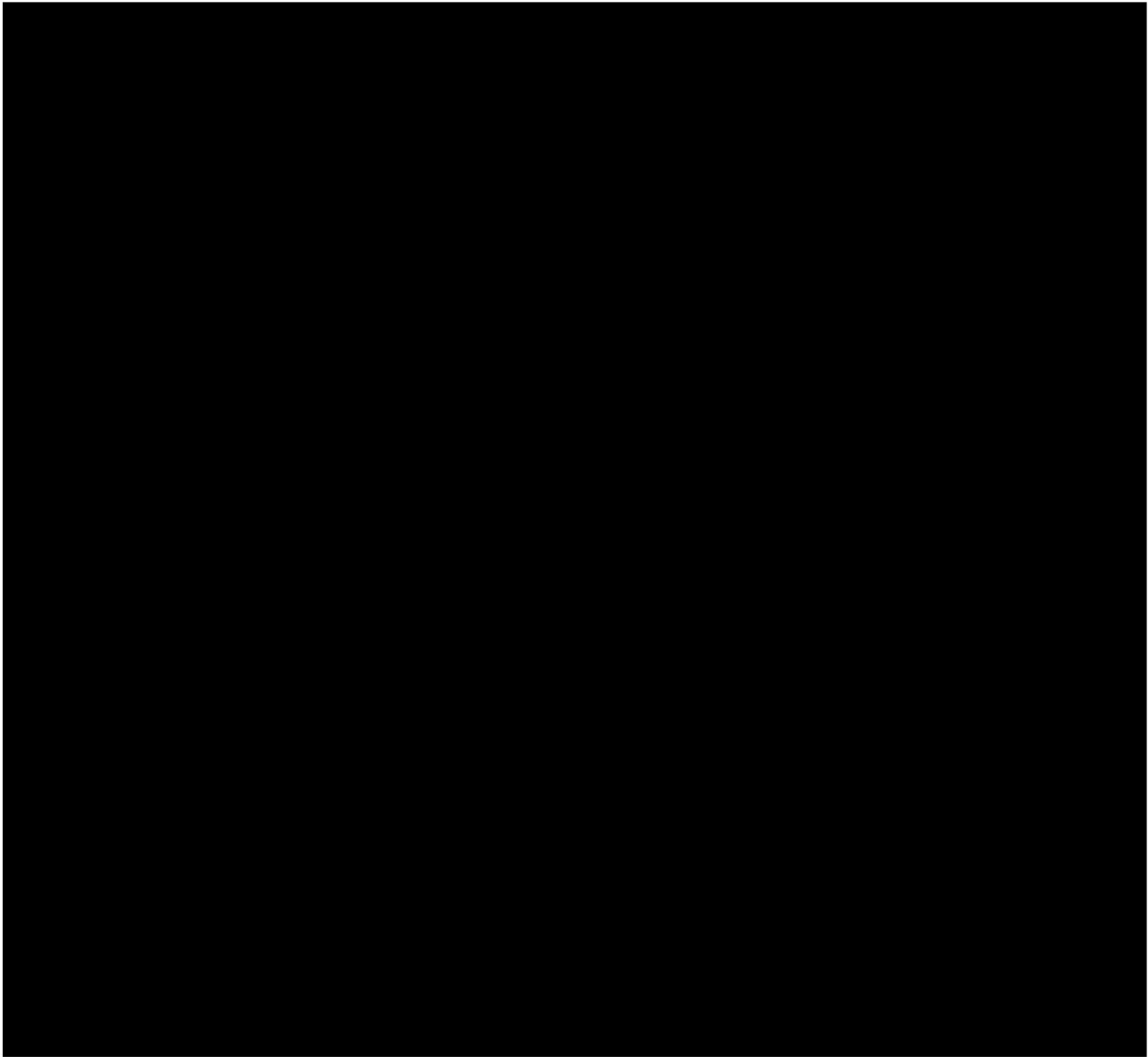
2.3.1 Rationale for evaluation of olaparib and ceralasertib in recurrent osteosarcoma

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[REDACTED]

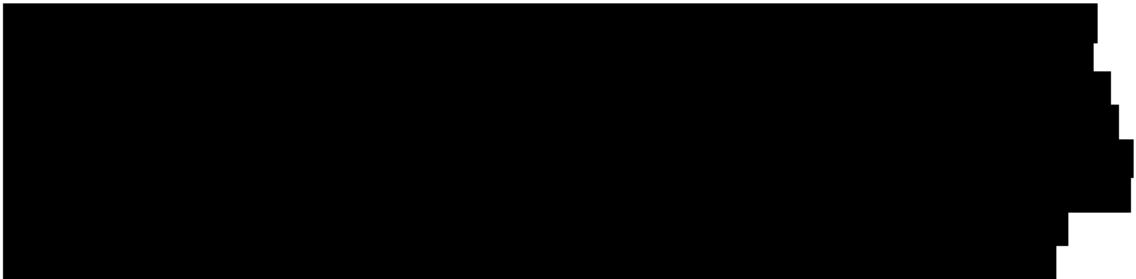
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[REDACTED]





2.3.2 Rationale for planned correlative studies



2.3.3 Rationale for evaluation of olaparib and ceralasertib in adolescent children





Specific genomic alterations will not be an eligibility criteria for participation in this clinical trial. Patient selection through testing of tumor samples for evidence of homologous recombination through somatic tumor profiling may limit the ability to determine biomarkers of response to combined PARP and ATR inhibition in this clinical trial. In addition, the tumor profiling assays available for clinical trial eligibility have not been validated to predict response to PARP inhibitor in osteosarcoma and may incorrectly select cases with the risks of either omitting patients with the potential to benefit or including patients who will not benefit. The ability of cell free assays to detect the somatic structural events (rearrangements and deletions) which account for some of the inactivating events in BRCA1/2 in osteosarcoma is unclear. Furthermore, assessment of circulating tumor DNA in osteosarcoma has not been studied on a large-scale and it is unclear how tumor volume, metastatic status, and other factors may contribute to our ability to detect these alterations.

We estimate that approximately 50% of the study population enrolled on this trial will be less than 18 years old. This trial will enroll all eligible patients and extensive correlative studies are planned as part of the study to better understand the genomic events and other tumor characteristics that are associated with response to treatment with combined PARP and ART inhibition. In order to be eligible, all participants in this study must have disease that has relapsed or has become refractory to conventional therapy. This patient population has extremely limited treatment options and the combination treatment has the potential to benefit all patients who are enrolled.

2.3.4 Overall Summary of Rationale

The observed response to cisplatin in osteosarcoma, *in vitro* susceptibility of osteosarcoma cell lines to ATR and PARP inhibitors, and the presence of mutations in genes involved in DNA damage repair and response suggest that systematic evaluation of DDR inhibitors in osteosarcoma is warranted.

3. PARTICIPANT SELECTION

Prior to approaching a potential participant, treating sites should reserve a treatment slot by contacting the Study Coordinator. Upon reserving a treatment slot, an investigator may begin the informed consent process for that participant. Once informed consent has been obtained, the investigator may begin screening studies to confirm eligibility. Once all eligibility criteria have been satisfied, the investigator may enroll the participant according to Section 4.0.

Baseline laboratory tests and screening studies must be completed within 14 days prior to the date of enrollment. Laboratory tests used to meet eligibility requirements may be completed within 14 days prior to date of enrollment, but must be repeated prior to dosing on Cycle 1, Day 1 if obtained > 7 days prior to Cycle 1, Day 1. If repeat laboratory studies no longer meet eligibility requirements, the participant must not receive protocol therapy. In this case, required studies may be repeated again within 5 days. If these studies now meet eligibility requirements, the patient may proceed with protocol therapy, otherwise the

patient will be removed from study and replaced. Baseline disease assessments, such as MRIs, CT scans and nuclear medicine studies, must be performed within 14 days of the date of enrollment.

3.1 Eligibility Criteria

- 3.1.1 Provision of informed consent prior to any study specific procedures.
- 3.1.2 Age ≥ 12 years and ≤ 40 years
- 3.1.3 Weight ≥ 40 kg
- 3.1.4 Lansky/Karnofsky performance status $\geq 60\%$ for participants ≥ 16 years of age and Lansky $\geq 60\%$ for participants < 16 years of age (see Appendix B) within 28 days prior to enrollment with no deterioration over the previous 2 weeks. Please note, patients who have had prior orthopedic surgery as part of their osteosarcoma therapy should not be considered non-ambulatory in their performance status if their non-ambulatory status is the result of surgery.
- 3.1.5 Estimated life expectancy of ≥ 16 weeks.
- 3.1.6 Diagnosis requirement
 - 3.1.6.1 All participants must have histologic verification of osteosarcoma at original diagnosis or relapse
 - 3.1.6.2 All participants must have disease that has relapsed or has become refractory to conventional therapy
- 3.1.7 Cohort 1 Requirements
 - 3.1.7.1 Participants must have measurable disease according to RECIST v1.1. At least one measurable lesion that can be accurately assessed at baseline by computed tomography (CT) (magnetic resonance imaging [MRI] where CT is contraindicated) and is suitable for repeated assessment as per RECIST v1.1.
 - 3.1.7.2 Surgical resection of all possible sites of disease is not feasible or will result in major and / or unacceptable morbidity and no other standard of care treatment is available per assessment of the treating investigator
 - 3.1.7.3 Participants must have archival tumor specimen available for submission. See section 9.2.2.1 for minimum specimen requirements for participation
- 3.1.8 Cohort 2 Requirements
 - 3.1.8.1 Participants must have had at least one episode of disease recurrence currently limited to the lung parenchyma with no limits on the number of episodes of recurrence
 - 3.1.8.2 Surgical resection of all possible sites of suspected pulmonary metastases in order to achieve a complete remission is considered feasible by treating physicians
 - 3.1.8.3 Participants with pulmonary disease on only one side must have archival tumor specimen available for submission. See section 9.2.2.1 for minimum specimen requirements for participation
- 3.1.9 Participants must have fully recovered from the acute toxic effects of all prior anti-cancer therapy. Participants must meet the following minimum washout periods prior to registration:
 - 3.1.9.1 Myeloid growth factors: At least 14 days following the last dose of long-acting growth factor (e.g. Neulasta) or 7 days following short-acting growth factor.

- 3.1.9.2 Stem Cell or Autologous T Cell Infusion: At least 42 days must have elapsed after stem cell or autologous T cell infusion.
- 3.1.9.3 Participants must not have previously received and progressed on olaparib or other PARP inhibitor therapy.
- 3.1.9.4 Participants must not have previously received and progressed on ceralasertib or other ATR inhibitor therapy.
- 3.1.10 Participants must have normal organ function as defined below.

3.1.10.1 Bone Marrow Function

- Absolute neutrophil count $\geq 1,250/\mu\text{L}$
- Platelets $\geq 100,000/\mu\text{L}$ (with no platelet transfusions within the last 28 days)
- Hemoglobin $\geq 9 \text{ g/dL}$ (with no blood transfusion or erythropoietin use within past 28 days)

3.1.10.2 Hepatic Function

- Total bilirubin $\leq 1.5 \times \text{ULN}$ unless the patient has documented Gilbert's syndrome
- AST or ALT $\leq 2.5 \times \text{ULN}$, unless liver metastases are present in which case they cannot be $> 5 \times \text{ULN}$

3.1.10.3 Renal Function

- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
12 to <13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

OR

- Creatinine clearance $\geq 70 \text{ mL/min/1.73 m}^2$ for participants with creatinine levels above institutional normal

- 3.1.11 Participants must be able to swallow intact pills.
- 3.1.12 Female participants must have a negative serum or urine pregnancy test within 28 days of study treatment and confirmed prior to treatment on Cycle 1 Day 1.
- 3.1.13 Females must not be breast feeding. Women of childbearing potential and their partners, who are sexually active, must agree to the use of 1 highly effective form of contraception and their partners must use a male condom (as described in section 5.4.5) from the signing of the informed consent, throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse.

- 3.1.14 Male patients who are sexually active must be willing to use barrier contraception for the duration of the study and for 1 week after the last study drug administration, with all sexual partners. Male patients must use a condom during treatment and for 6 months after the last dose of study drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential and must not donate sperm for 6 months after the last dose of study drug. Female partners of male patients should also use a highly effective form of contraception (as described in section 5.4.5) for 6 months after the last dose of study drug(s) if they are of childbearing potential. True abstinence for either sex is an acceptable form of contraception and must be documented as such.
- 3.1.15 Ability to understand and/or the willingness of the patient (or parent or legally authorized representative, if minor) to provide informed consent, documented using an institutionally approved informed consent procedure.
- 3.1.16 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

3.2 Exclusion Criteria

- 3.2.1 Participants with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) or features suggestive of MDS/AML.
- 3.2.2 Patients with a known diagnosis of ataxia telangiectasia.
- 3.2.3 Cytotoxic chemotherapy, hormonal or non-hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted (a duration of five half times is allowed for patients treated with non-cytotoxic drugs).
- 3.2.4 Immunotherapy within 42 days of Cycle 1 Day 1.
- 3.2.5 Prior TOTAL lung radiation. If prior radiation included lung then radiation must have been completed 12 weeks before Cycle 1 Day 1 AND V20 (% of lung that received 20Gy) must not exceed 25% OR the mean lung dose must be less than 5Gy. Even if these eligibility criteria are met, patients who have received prior radiotherapy including lung are only eligible after review and approval by the study PI.
- 3.2.6 Palliative radiotherapy to sites not including lung must have been completed 7 or more days before Cycle 1 Day 1 (with the following exception: patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation must have been completed 4 weeks before C1D1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 5 days prior to the study treatment.
- 3.2.7 Receiving, or having received during the 14 days prior to Cycle 1 Day 1, corticosteroids (at a dose > 10 mg prednisone/day or equivalent) for any reason. Topical, inhaled or ophthalmic steroid administration is acceptable.
- 3.2.8 Major surgery within 2 weeks of starting study treatment: patients must have recovered from any effects of any major surgery.

- 3.2.9 Any other malignancy which has been active or treated within the past three years, with the exception of cervical intra-epithelial neoplasia and non-melanoma skin cancer, Ductal Carcinoma in Situ, stage 1 grade 1 endometrial carcinoma, or other solid tumors curatively treated with no evidence of disease for ≥ 5 years prior to study entry.
- 3.2.10 With the exception of alopecia and CTCAE grade 2 neuropathy, any unresolved toxicities from prior therapy $\geq$ Common Terminology Criteria for Adverse Events (CTCAE) grade 2.
- 3.2.11 Patient with resting left-ventricular ejection fraction (LVEF) $< 50\%$ measured by ECHO/MUGA
- 3.2.12 Any of the following cardiac diseases currently or within the last 6 months (by New York Heart Association (NYHA) $\geq$ Class 2 where applicable):
- Unstable angina pectoris
 - Congestive heart failure or known reduced LVEF $< 50\%$
 - Acute myocardial infarction
 - Conduction abnormality not controlled with pacemaker or medication e.g. complete left bundle branch block, third degree heart block
 - Significant ventricular or supraventricular arrhythmias e.g. (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
 - Patients at risk of brain perfusion problems, e.g., medical history of carotid stenosis or pre-syncopal or syncopal episodes, history of TIAs
 - Uncontrolled hypertension (grade 2 or above) requiring clinical intervention
- 3.2.13 Corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs) 2-5 minutes apart using the Fredericia formula
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as congestive heart failure, unstable angina pectoris, acute myocardial infarction, hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age, conduction abnormality not controlled with pacemaker or medication.
- 3.2.14 Patients with relative hypotension (less than 5th percentile for age/height/sex or systolic and/or diastolic blood pressure $>15\%$ below baseline) or clinically relevant orthostatic hypotension (a fall in systolic blood pressure of at least 20 mm Hg within 3 minutes of standing compared to blood pressure obtained from sitting/supine position).
- 3.2.15 Concomitant use of known potent cytochrome P (CYP) 3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is five half-lives.
- 3.2.16 Concomitant use of known potent (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is five half-lives, except for St-Johns' wort, which is 3 weeks (See appendix E).

Patient has had prescription or non-prescription drugs or other products known to be CYP3A4 and/or CYP2B6 substrates or CYP3A4 and/or CYP2B6 substrates with a narrow therapeutic index. Exposure of other drugs metabolised by CYP3A4 and/or CYP2B6 may be reduced and additional monitoring may be required (see Appendix E).

The use of herbal supplements or 'folk remedies' (and medications and foods that significantly modulate CYP3A activity) should be discouraged. If deemed necessary, such products may be administered with caution and the reason for use documented in the CRF. Please see Appendix E for further details.

- 3.2.17 Planned herbal medications use within 7 days prior to first dose of study treatment.
- 3.2.18 Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of ceralasertib.
- 3.2.19 Participants with a known hypersensitivity to olaparib or any of the excipients of the product or any contraindication to the combination anti-cancer agent as per local prescribing information.
- 3.2.20 Participants with a known hypersensitivity to ceralasertib or any of the excipients of the product or any contraindication to the combination anti-cancer agent as per local prescribing information.
- 3.2.21 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.22 As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases that places the patient at unacceptable risk of toxicity or non-compliance. Examples include, but are not limited to, active bleeding diatheses, renal transplant, uncontrolled major seizure disorder, severe COPD, superior vena cava syndrome, extensive bilateral lung disease on High Resolution CT scan, severe Parkinson's disease, active inflammatory bowel disease, psychiatric condition, or active infection including any patient known to have hepatitis B, hepatitis C and human immunodeficiency virus (HIV) or requiring systemic antibiotics, antifungals or antiviral drugs. Screening for chronic conditions is not required.
- 3.2.23 Patients with symptomatic uncontrolled brain metastases. Patients with a history of treated central nervous system (CMS) metastases are eligible provided they meet all of the following criteria: disease outside the CNS is present, no clinical evidence of progression since completion of CNS-directed therapy, minimum 3 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade $\geq$ 3) acute toxicity with no ongoing requirement for >10 mg of prednisolone per day or an equivalent dose of other corticosteroid. If on corticosteroids, the patient should be receiving a stable dose of corticosteroids, started at least 4 weeks prior to treatment.
- 3.2.24 Female patients who are pregnant or breast-feeding.
- 3.2.25 Male or female patients of reproductive potential who are not employing an effective method of birth control.

3.2.26 Spinal cord compression or brain metastases unless treated, asymptomatic and stable and not requiring steroids for at least 4 weeks prior to start of study treatment.

3.3 Inclusion of Children and Minorities

3.3.1 Both male and female children of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Sites

Dana-Farber/Harvard Cancer Center study staff will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and will complete and sign the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber by the Study Coordinator (or designee). All sites should contact the Study Coordinator to verify an available slot before initiating the informed consent and screening processes (see Section 3). See Appendix C for a list of study sites.

Following registration, participants may begin protocol therapy and should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following de-identified documents should be e-mailed to the Study Coordinator:

- Copy of the following source documents confirming eligibility:
 - Eligibility lab results in Section 3.1.9
 - Pathology report confirming diagnosis of osteosarcoma
 - Imaging and/or pathology and/or surgical reports demonstrating measurable disease (Cohort 1) or resectable disease limited to the lung parenchyma (Cohort 2) preferably from the most recent imaging time point

- Most recent clinician note, including medication list, height, and weight and performance score
- Signed participant consent form
- HIPAA Authorization form
- Protocol-specific eligibility checklist signed by site investigator.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity.

The research nurse or data manager at the participating site will then contact the Study Coordinator to verify eligibility. To complete the registration process, the Study Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. The Study Coordinator will e-mail the participant study number to the participating site in a registration e-mail. The site must receive this registration e-mail prior to initiating protocol therapy. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

5. TREATMENT PLAN

5.1 Treatment Regimen

5.1.1 Overview of Treatment Regimen

Study treatment will be administered in 28 day cycles.

As of v4, participants will receive olaparib at a dose of 150mg orally twice a day (BID) on days 1-28 of a cycle.

As of v4, participants will receive ceralasertib at a dose of 80mg orally twice a day on days 1-14 of a cycle.

Participants may begin therapy on any day of the week, though treating sites are advised to note the timing of required pharmacokinetic blood draws when planning the start of the first cycle (See Section 9.1).

Participants in cohort 2 will undergo surgical resection of lung metastases according to the study schema (protocol page 5). Participants should resume protocol therapy as soon as healing is adequate, typically between day 14 and 21 post-operatively. Participants who are not able to begin or resume protocol therapy by day 21 post-operatively will be removed from study.

Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

In the absence of criteria for removal from protocol therapy (see Section 5.5), participants may continue to receive study treatment for up to 24 cycles (approximately 2 years of therapy).

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

If screening laboratory studies for registration were obtained > 7 days prior to Cycle 1, Day 1, then the following laboratory studies must be repeated within 7 days of Cycle 1, Day 1:
CBC with differential, BUN, Cr, Bilirubin, ALT, AST.

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

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

A 12-lead ECG will be performed in triplicate at screening.

The timing and number of ECGs may be adjusted in response to the emerging PK and safety profile. Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point 3 ECG recordings should be taken at about 5 minute intervals. A standardised ECG machine should be used and the patient should be examined using the same machine throughout the study, where feasible.

After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded.

If any of these repeat laboratory studies do not meet organ function requirements in Section 3.1.8, then the participant must not receive protocol therapy. In this case, required studies may be repeated again within 5 days. If these laboratory studies now meet eligibility requirements, the patient may proceed with protocol therapy, otherwise the patient will be removed from study and replaced.

5.2.2 Subsequent Cycles

Prior to the start of each cycle of therapy, participants must have the following laboratory evaluations:

- CBC with differential
- Glucose
- Sodium
- Potassium
- Calcium
- Magnesium
- BUN
- Creatinine
- Total bilirubin
- AST
- ALT
- GGT
- LDH

The laboratory values must meet all of the following criteria to start the cycle:

- No clinical or radiographic evidence of disease progression
- Participants has not experienced an event meeting criterion for removal from protocol therapy (see section 5.5)
- Absolute neutrophil count $\geq 1000/\mu\text{L}$
- Platelets $\geq 75,000/\mu\text{L}$ and transfusion independent, defined as no transfusion in the 7 days prior to the laboratory test to confirm criteria
- Total bilirubin $\leq 1.5 \times$ upper limit of normal for age
- ALT (SGPT) $\leq 2.5 \times$ upper limit of normal (for the purpose of this study, the ULN for ALT is 45 U/L)
- AST (SGOT) $\leq 2.5 \times$ upper limit of normal
- Adequate renal function defined as:
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
12 to <13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

OR

- Creatinine clearance $\geq 70 \text{ mL/min/1.73 m}^2$ for participants with creatinine levels above institutional normal.

Laboratory studies must be obtained within 3 days of Day 1 of each cycle. Imaging studies, when required per protocol, must be obtained within 7 days of Day 1 of each cycle.

If a participant does not meet criteria to start subsequent cycles of therapy then assessments including laboratory studies and physical exam (if applicable) should be repeated at a suggested interval of twice weekly (every 3-4 days) until the patient meets criteria to begin the subsequent cycle as defined above, and/or meets criteria for a dose modification (See Section 6), and/or meets criteria to come off protocol therapy (See Section 5.5).

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 6.1.1.3.

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

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

5.3 Agent Administration

5.3.1 Olaparib

Olaparib is administered orally twice a day (BID) on days 1-28 of a cycle.

Olaparib will be dispensed to participants on Day 1 of each cycle until the participant completes the study, withdraws from the study or closure of the study.

Doses are administered orally BID approximately 12 hours apart on Day 1 through 28 of each 28-day cycle. Olaparib tablets should be taken at approximately the same time on each dosing day. Dosing around a window of +/- 2 hours from scheduled time will not be considered a deviation. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If a cycle is extended past Day 28 (up to +3 days) for scheduling reasons, olaparib should be continued.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced only if all remaining tablets can be seen and counted. Should any participant enrolled on the study miss a scheduled dose for whatever reason (e.g. forgetting to take the tablets or vomiting) or need to modify the timing of a scheduled dose for any reason, the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. The dose should not be taken more than 2 hours in advance of the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the participant should take their allotted dose at the next scheduled time. Doses should not be taken fewer than 10 hours apart.

Olaparib drug product should be stored within the temperature range stated on the label. Participants should be instructed to store the drug product at home in the provided container and to keep out of the reach of children.

Olaparib tablets will be supplied by AstraZeneca and distributed in compliance with local regulatory requirements (See Section 8 for details of drug supply).

Each dose of Olaparib will be recorded in a medication diary (Appendix D). The medication diary will be returned to clinic staff at the end of each cycle.

In the absence of safety data in pregnant animals or humans, olaparib should not be dispensed by a pregnant woman. Caregivers should use caution when cleaning up emesis, with the use of gloves recommended.

Patients are prohibited from consuming grapefruit juice or Seville oranges (including marmalade, juice, etc) while participating in the study.

5.3.2 Ceralasertib

Ceralasertib is administered orally twice a day on days 1-14 of a cycle.

Ceralasertib will be dispensed to participants on Day 1 of each cycle until the participant completes the study, withdraws from the study or closure of the study.

Doses are administered orally twice a day approximately 12 hours apart on Day 1 through 14 of each 28-day cycle. Ceralasertib should be taken at the same time as the olaparib morning and evening doses. Ceralasertib should be taken at approximately the same times on each dosing day. Dosing around a window of +/- 2 hours from scheduled time will not be considered a deviation. The ceralasertib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

- Patients must fast (water to drink only) from at least 2 hours prior to taking their ceralasertib dose to at least 1 hour post-dose for all doses. No fasting restrictions apply when olaparib is taken on its own.
- If vomiting occurs shortly after ceralasertib is swallowed, the dose should only be replaced if all of the intact tablets can be counted and then treatment resumed with the following scheduled dose. The scheduled dose can be taken up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken and patient should continue with next dose at allotted time.
- If no clinically significant blood pressure (BP) changes are seen following the single dose, then no restrictions with regard to driving are required.
- For all patients, it is prohibited to consume grapefruit juice or Seville oranges (including marmalade, juice, etc.) while participating in the study.
- Precautions are advised as a lifestyle recommendation when outside in the sun e.g. limiting the duration of sun exposure, wearing protective clothing (hat and sunglasses) and sunscreen.

Ceralasertib drug product should be stored within the temperature range stated on the label. Participants should be instructed to store the drug product at home in the provided container and to keep out of the reach of children.

Ceralasertib tablets will be supplied by AstraZeneca and distributed in compliance with local regulatory requirements (See Section 8 for details of drug supply).

Each dose of ceralasertib will be recorded in a medication diary (Appendix D). The medication diary will be returned to clinic staff at the end of each cycle.

In the absence of safety data in pregnant animals or humans, ceralasertib should not be dispensed by a pregnant woman. Caregivers should use caution when cleaning up emesis, with the use of gloves recommended.

5.4 General Concomitant Medication, Supportive Care Guidelines and Contraception

5.4.1 Concomitant Surgery

Although not encouraged, participants in Cohort 1 who achieve a partial response or have stable disease following the pre-Cycle 5 evaluation time point that is **confirmed** with imaging performed 4 weeks later will be allowed to undergo resection of sites of disease and remain on protocol therapy. Therapy will be held during surgery and resumed upon recovery from surgery, but at least 2 weeks after surgery. If the participant has not recovered from surgery within 6 weeks the participant will go off protocol therapy. If surgery is performed in a participant who does not achieve a **confirmed** partial response or have **confirmed** stable disease, the participant will go off protocol therapy.

5.4.2 Palliative radiotherapy

Although not encouraged, participants in Cohort 1 who achieve a partial response or have stable disease

following the pre-Cycle 5 evaluation time point that is **confirmed** with imaging performed 4 weeks later, will be allowed to undergo palliative radiotherapy and remain on protocol therapy. Palliative radiotherapy including lung parenchyma is not allowed. Radiation to more than 30% of the bone marrow or with a wide field is not allowed. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes palliative radiation treatment and for the duration of radiotherapy treatment and study treatment should be restarted within 4 weeks after completion of palliative radiotherapy as long as any bone marrow toxicity has recovered.

5.4.3 Concomitant Medications

The use of any natural/herbal products or other “folk remedies” 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. Patients should comply with the concomitant treatment information described in the study protocol.

Medications that should NOT be administered:

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) and stable treatment of > 6 months with LHRH analogues are acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

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.

If the use of any potent inducers or inhibitors of CYP3A4/5 are considered necessary for the patient's safety and welfare, the investigator must contact the Overall PI. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT)) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Administration of other anti-cancer agents

Patients should not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form. In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the CRF. Further details on concomitant medication restrictions for treatment with olaparib and ceralasertib can be found in the latest version of the olaparib and ceralasertib Investigator's brochures.

Ceralasertib

Ceralasertib is an investigational drug for which no data on *in vivo* interactions are currently available. Potential interaction is considered on the basis of preclinical *in vitro* data only.

The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in Appendix E. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with ceralasertib is safe. If ceralasertib is being administered in combination, potential interactions of the combination partner should also be considered.

- The principal enzyme for metabolizing ceralasertib is CYP3A. Subjects should avoid concomitant drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A activity from the time they enter the screening period until 28 days after the last dose of study treatment.
- Prior to study medication, use of potent inducers or inhibitors of CYP3A are not permitted. Refer to section 3.2 and Appendix E for information on required wash-out periods before starting study medication.
- On study medication, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYP3A, the investigator must interrupt ceralasertib for the duration of the potent CYP3A inhibitor and wait for the required wash-out period before dosing ceralasertib again. If potent CYP3A inducers are considered necessary for the patient's safety and welfare, this may diminish the clinical efficacy of ceralasertib and the patient should be monitored carefully for any change in the efficacy of study treatment. Refer to Appendix E and Section 3.2 for additional guidance.
- Ceralasertib is a Pgp substrate. Co-administration of Pgp inhibitors or inducers may affect exposure to ceralasertib and, therefore, should not be co-administered with ceralasertib. If the use of any inhibitors or inducers of Pgp are considered necessary for the subject's safety and welfare, the investigator must interrupt ceralasertib for the duration of the Pgp inhibitor or inducer and wait for the required wash-out period of the Pgp modulator (five half-lives) before dosing ceralasertib again. Refer to Appendix E and section 3.2 for additional guidance.
- Ceralasertib is also a substrate of BCRP. Co-administration of BCRP inhibitors or inducers may affect exposure to ceralasertib; therefore, it is recommended that the investigators must interrupt ceralasertib for the duration of the BCRP inhibitor or inducer and wait for the required wash-out period of the BCRP modulator (five half-lives) before dosing ceralasertib again. Refer to Appendix E for additional guidance.
- Ceralasertib is a potential inducer of CYP3A4 and CYP2B6. Caution should be applied with coadministration of drugs that are either completely metabolized by CYP3A4 and/or CYP2B6, or that are substrates of CYP3A4 and/or CYP2B6 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolized by CYP3A4 and/or CYP2B6 may be reduced. Refer to Appendix E for additional guidance.
- Ceralasertib is an inhibitor of OATP1B1 and BCRP. Caution should be applied with coadministration of substrates of OATP1B1 and/or BCRP as ceralasertib may increase their exposure. Refer to Appendix E for additional guidance.
- Primary G-CSF and erythropoietin use is not allowed. Secondary G-CSF may be used if required.

- Investigators should also note specific restrictions relating to the combination agent according to the local prescribing information.

OlaparibStrong or Moderate CYP3A Inhibitors

Known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with study treatment.

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

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

Strong or Moderate CYP3A Inducers

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

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

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

Permeability glycoprotein (P-gp) inhibitors

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

Effect of Olaparib on Other Drugs

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

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

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

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

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozone, sirolimus, tacrolimus and quetiapine.
- CYP2B6 – bupropion, efavirenz.
- CYP2C9 – warfarin.
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin.
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine.
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan.
- OCT2 - serum creatinine.

5.4.4 Supportive Care Guidelines

5.4.4.1 Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary

5.4.4.2 Antiemetics: participants administered study therapy should be monitored for GI toxicities and receive supportive treatment as clinically appropriate

5.4.4.3 Participants administered study therapy should be monitored in order to detect and treat mucositis/stomatitis early before it becomes severe

5.4.5 Contraception

- Male patients
 - Men must use a condom (with spermicide) during the study, and for 1 week after the last dose of study drug, with all sexual partners
 - Where a sexual partner of a male participant is a 'woman of child-bearing potential' who is not using effective contraception, men must use a condom (with spermicide) during the study and for 6 months after the last dose of a study drug
 - Must not donate sperm throughout the period of taking study drug(s) and for 6 months after the last dose of study drug
- Female patients
 - Women with evidence of non-child-bearing potential at screening (Section 4 have no restrictions around contraception
 - Women of child-bearing potential and their partners, who are sexually active, must use ONE highly effective forms of contraception (as listed below) AND their partners must use a male condom. This should be started from the signing of the informed

consent and continue throughout the period of taking study treatment for at least 6 months after the last dose of study drug, with all male sexual partners. Contraceptives that are prone to drug-drug interactions may not be effective due to a potential CYP3A4 interaction with ceralasertib.

- Medroxyprogesterone injections (e.g., Depo-provera)
- Intrauterine Device (IUD)
- Levonorgestrol Intrauterine System (e.g., Mirena)
- Tubal occlusion
- Vasectomised partner

True abstinence will be an acceptable form of contraception for both sexes.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. Study treatment may continue for up to 24 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Toxicity requiring dose modification that meets criteria for removal from protocol therapy (see Section 6)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Failure to recover from surgery within 6 weeks after surgery
- Surgery performed in a patient who has not achieved a confirmed complete or partial response
- Bone marrow findings consistent with AML or MDS
- Development of another malignancy
- Pregnancy

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI (see section 7.5.1).

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.6 Duration of Follow Up

Participants will be followed for 2 years from last dose of study drug or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Completion of planned follow-up;
- Found to be ineligible, including participants who have repeat organ function laboratory studies obtained within 7 days of Cycle 1, Day 1 that do not meet entry eligibility requirements;
- Lost to follow-up;
- Withdrawal of consent for data submission;
- Death.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSE DELAYS / DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following text and table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for guiding dose delays and dose modifications.

6.1 General Guidance

Toxicity will be graded using the CTCAE criteria, version 5.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

Any clinically significant and/or unacceptable toxicity observed during the course of the study should be managed in the first instance by interruption of the dose of study treatment, dose reductions if necessary and administration of supportive therapy.

If the toxicity resolves or reverts to $\leq$ CTCAEv4 grade 1 or 2 (depending on the toxicity, see **Table 3** below) treatment with ceralasertib and/or olaparib may be restarted using the rules in section 6.1.1 for dose modifications. Patients who are at the lowest possible dose, or who have their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

If the toxicity does not resolve to $\leq$ CTCAEv4 grade 1 or 2 (depending on the toxicity) or the patient is not showing clinical benefit, then the patient should be discontinued from treatment and observed until resolution of the toxicity.

Repeat dose interruptions are allowed as required for a maximum of 28 days on each occasion as recommended in **Table 3**. If the duration of ceralasertib or olaparib dose interruption is longer than 28 days, the case should be discussed with the Overall Principal Investigator.

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 28 days for resolution of

intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Overall PI. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery and restarted 10 days post-surgery if the wound has healed. If the wound has not healed well, a further 14 days may be allowed and the patient can recommence study treatment if there is no evidence of disease progression based on the clinical judgement. No stoppage of study treatment is required for any biopsy procedure.

If either one of ceralasertib or olaparib is permanently discontinued, then the other compound should also be permanently discontinued.

6.1.1 Guidance for dose modification and interruption

Refer to Table 3, Table 4 and Table 5 for dose modification and stopping criteria for ceralasertib and olaparib. Please note that for simultaneous toxicities (for example, anemia and neutropenia), the event should be considered singular and no further dose modification should be made providing that both toxicities resolve within 28 days. However, sequential toxicities (for example, anemia followed by neutropenia) should follow the guidance below; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle. Once dose is reduced, escalation is not permitted.

Table 3. Dose interruption and stopping criteria for ceralasertib and olaparib

Event	Action
Grade 1-2 neutropenia or Grade 1 thrombocytopenia	Ceralasertib and olaparib dosing may continue if neutrophil count is $\geq 1000/\text{mm}^3$ and/or platelet count is $\geq 75,000/\text{mm}^3$
Grade 1-2 toxicities (except neutropenia and thrombocytopenia)	Investigator decision whether to interrupt ceralasertib and/or olaparib (max 28 days) or continue treatment. Treatment may be resumed at the same dose level prior to interruption.
Grade 3 neutropenia or Grade 3 anaemia	Interrupt ceralasertib and olaparib (max 28 days) and give appropriate supportive treatment e.g. transfusion, until AE improves to at least neutrophil count $\geq 1000/\text{mm}^3$ and hemoglobin $\geq 8.0 \text{ g/dL}$, then restart reducing the dose of ceralasertib by 1 level.
Grade 2-3 thrombocytopenia	First occurrence Interrupt ceralasertib only (max 28 days) and give appropriate supportive treatment until platelets improve to at least $\geq 75,000/\text{mm}^3$. At resolution, it is not mandatory to lower the dose as blood counts may recover during the “off period” on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, ceralasertib should be restarted with a dose reduction by 1 level for ceralasertib. Subsequent occurrences Interrupt ceralasertib only (max 28 days) and give appropriate supportive treatment until platelets improve to at least $\geq 75,000/\text{mm}^3$. At resolution, it is not mandatory to lower the dose as blood counts may recover during the “off period” on the

	intermittent schedule. If blood counts do not recover by the start of the next dosing period, ceralasertib should be restarted with a dose reduction by 1 level for ceralasertib or it is at investigator discretion to stop treatment.
Grade 4 thrombocytopenia	Interrupt ceralasertib and olaparib (max 28 days) and give appropriate supportive treatment; investigator discretion on whether to restart treatment with a dose reduction by 1 dose level for both drugs or stop treatment when the platelet count has recovered to $\geq 75,000/\text{mm}^3$.
Grade 3-4 toxicity (except grade 3 anaemia, grade 3 neutropenia and grade 3-4 thrombocytopenia)	First occurrence Interrupt ceralasertib and /or olaparib (max. 28 days) and given appropriate supportive treatment; restart treatment with a dose reduction by 1 level for ceralasertib and/or olaparib when the toxicity is resolved (grade ≤ 1 or 2 depending on the toxicity or returns to baseline). Subsequent occurrences Interrupt ceralasertib and /or olaparib (max 28 days) and give appropriate supportive treatment. Investigator discretion whether to restart treatment with a reduced dose of ceralasertib and/or olaparib or to stop treatment.
Surgery	Interrupt study treatment (maximum 28 days), resume at full dose. Study treatment should be stopped 3 days prior to surgery and resumed approximately 10 days later. If the wound has not healed a further 14 days are permitted prior to restarting study treatment. No stoppage is required for biopsy procedures.
Vomiting	If vomiting occurs shortly after ceralasertib is swallowed, the dose should only be replaced if all of the intact capsules can be counted. Resume with the following scheduled dose.
Missed dose	Allowed to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken, and patient should continue with next dose at allotted time.

Table 4. Dose reduction levels for ceralasertib

Initial dose	80 mg twice daily days 1–14
Level 1 dose reduction	80 mg twice daily days 1–10
Level 2 dose reduction	80 mg twice daily days 1–7
Level 3 dose reduction	Stop treatment

Table 5. Dose reduction levels for olaparib

Initial dose	150 mg twice daily
Level 1 dose reduction	100 mg twice daily

Level 2 dose reduction	Stop treatment
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Individual stopping criteria:

Hepatic

ALT or AST or ALP* > 5 x ULN

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

[ALT or AST > 3 x ULN] and [total bilirubin > 2 x ULN or INR+ > 1.5 or other evidence of impairment to the synthesis function of the liver]

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

+ Unless patient is receiving warfarin

Please refer to Appendix A “Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy’s Law.”

Cardiovascular

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

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

6.1.2 Management of cardiovascular abnormalities

Cardiovascular toxicity is potentially associated with ceralasertib. Either clinically significant hypotension (defined as an asymptomatic decrease of more than 20 mmHg in systolic blood pressure to below 70 mmHg persisting for at least 10 minutes) or symptomatic orthostatic fall in systolic blood pressure (of more than 20 mmHg compared to resting supine systolic blood pressure) should be monitored for and managed with drug interruptions or reductions as per investigator’s discretion. Other cardiovascular safety measures e.g. ECG readings should be considered as well.

6.1.3 Additional olaparib toxicity management

6.1.3.1 Management of anemia

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

Management of neutropenia, leukopenia and thrombocytopenia

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. For toxicity of grades 1-2 especially if more than one toxicity is present then drug can be interrupted at investigator discretion.

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

Platelet transfusions, if indicated, should be done according to local hospital guidelines. For cases where patients develop prolonged hematological toxicity (>2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section below on “Management of prolonged hematological toxicities while on study treatment.”

Management of prolonged hematological toxicities while on study treatment:

If a patient develops prolonged hematological toxicities such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, consider referral to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome (MDS) or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Study treatment should be discontinued if patient’s diagnosis of MDS and/or Acute Myeloid Leukemia (AML) is confirmed.

6.1.3.2 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If study treatment cannot be restarted within 4 weeks, then the patient must permanently discontinue study treatment. If the interruption is any longer than this the Overall PI must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

6.1.3.3 Management of new or worsening pulmonary symptoms

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

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

- Physical examination; Signs and symptoms (cough, shortness of breath and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO₂; Saturation of peripheral oxygen (SpO₂)
- Other items; When pneumonitis (interstitial lung disease [ILD]) is suspected during study treatment, the following markers should be measured where possible:
 - (i) ILD markers (KL-6, SP-D) and β -D-glucan
 - (ii) Tumor markers: Particular tumor markers which are related to disease progression.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these should be discussed with the Overall PI and treatment should not be resumed.

6.1.3.4 Management of nausea and vomiting

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

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie 2 pieces of toast or a couple of biscuits). As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg, dopamine receptor antagonist, antihistamines or dexamethasone.

6.1.3.5 Management of diarrhea

Vigorous anti-diarrheal treatment loperamide (Imodium) is required at the **first** onset of diarrhea according to American Society of Clinical Oncology (ASCO) guidelines. Oral loperamide (Imodium) 4 mg should be administered at the first onset of diarrhea and then 2 mg every 2 hours until diarrhea-free for at least 12 hours. The first dose of loperamide could be lowered to 2 mg if the diarrhea is recurrent and if, in the opinion of the treating physician, the diarrhea is not severe.

Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhea within 24 hours of using loperamide or other prescribed anti-diarrheal medications. If diarrhea is severe (ie, requiring intravenous [IV] rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for IV hydration and correction of electrolyte imbalances.

6.1.3.6 Renal and hepatic impairment

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be

avoided see Section 5.4.

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

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 mL/min) for any reason during the course of the study: the dose of study treatment should be reduced to 200mg BD.

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

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

Olaparib can be administered to patients with mild hepatic impairment (Child-Pugh classification A) with no dose adjustment. It is recommended that olaparib is not given to patients with moderate or severe hepatic impairment as data are not available in these patients.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Introduction to Adverse Event Reporting

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the study treatment.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.2) and the characteristics of the observed AE (Section 7.3) will determine whether the event requires expedited reporting **in addition** to routine reporting. Please Refer to section 7.6 for determination of expectedness for SUSAR reporting.

7.2 Adverse Event List for the combination of olaparib and ceralasertib

Please refer to the ceralasertib IB and the Olaparib package insert and IB for comprehensive lists of reported adverse events and any potential risks associated with ceralasertib and Olaparib.

Greater than 50% Incidence

- Nausea
- Anemia

10-50% Incidence

- Thrombocytopenia
- Neutropenia
- Constipation

- Vomiting
- Diarrhea
- Fatigue
- Asthenia
- Pyrexia
- Decreased appetite
- Cough
- Dyspnea
- Dizziness
- Insomnia
- Pain (including abdominal pain and back pain)
- Headache

1-10% Incidence

- Rash
- Pruritis
- Musculoskeletal chest pain
- Intestinal obstruction
- Pleural effusion
- Pulmonary embolism
- Aspartate aminotransferase increased
- QTc prolonged
- Myelodysplastic syndrome/Acute myeloid leukemia (<1.5% with olaparib alone)
- Infection (urinary tract infection, respiratory tract infection, pneumonia)

<1% Incidence (rare but serious)

- Pneumonitis (olaparib alone)
- Cholangitis

7.3 Adverse Event Characteristics

Investigators are to provide the following adverse event characteristics for all adverse events experienced from enrollment until 30 days after last dose of study treatment:

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTAP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- Attribution of the AE:
 - 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.
- Seriousness of AE: An AE is classified “serious” (SAE) if it meets any of the following criteria:

Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (<i>e.g.</i> , sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An <u>important medical event</u> that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (<i>i.e.</i> , death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. NOTE: All Grade 3-5 infusion-related reactions are considered serious and require expedited reporting.

An AE that meets none of the above criteria is considered “non-serious”.

Note: Seriousness is independent of attribution or expectedness of the AE.

- Expectedness of the AE: In addition to term, grade, attribution, and seriousness, adverse events that have the potential to qualify for expedited reporting (see Section 7.5) are to be designated as “expected” or “unexpected”.

Olaparib and ceralasertib adverse events of special interest

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca.

Olaparib AEs of special interest

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

Ceralasertib AEs of special interest

There are no AESI for ceralasertib which require additional data collection.

7.4 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions to the Overall Principal Investigator on the toxicity case report forms. AE collection will begin following the participant's written consent to participate in the study. AEs that also meet criteria for expedited reporting (see Section 7.5) must also be reported in routine study data submissions.

All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such (see Section 7.5).

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

7.5 Expedited Adverse Event Reporting

7.5.1 Criteria for Expedited Adverse Event Reporting

Investigators **must** report to the Overall Principal Investigator in an expedited manner any adverse events (AE) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment if they meet any of the following criteria and are not listed as adverse events exempt from expedited reporting in Section 7.5.3:

- Serious adverse event, including grade 5 adverse events
- Pregnancy in a female participant who received study treatment (see section 7.6.3)
- Overdose of study treatment (see section 7.8.3)
- Potential Hy's Law (PHL) criteria met for liver injury (see Appendix A)
- Other adverse events (serious or not serious) that meet DFCI Institutional Review Board Adverse Event Reporting policy for expedited reporting (see table below):

Note: Grade 2 and Grade 3 laboratory abnormalities that are considered by the investigator to be clinically insignificant and do not require therapy, or adjustment in prior therapy, do not need to be reported to the Overall Principal Investigator or the DFCI IRB.

Regardless of treating institution, these expedited reports will be submitted to the Overall Principal Investigator using a DF/HCC AE Reporting form.

The treating institution must notify the Overall Principal Investigator by phone or email of any serious adverse event within 24 hours of learning of the event, with a formal written report within 3 business days.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure),

the relationship should be specified in the narrative section of the SAE Report Form.

For non-serious AE's that nevertheless meet the above DF/HCC definition for expedited reporting, the following timelines apply for submission of a DF/HCC AE Reporting form to the Overall Principal Investigator.

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	5 calendar days [#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days [#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study <i>or</i> for AEs occurring within 30 days of the last intervention, the AE should be reported within <u>1 business day</u> of learning of the event.					

7.5.2 Guidelines for MultiCenter Expedited AE Reporting

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any adverse event meeting the criteria for expedited reporting as defined in section 7.5.1.

Investigative sites within DF/HCC will report expedited AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report expedited AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. These sites will also complete a DF/HCC AE Reporting form to the Overall Principal Investigator within the timeframes detailed above. The Overall Principal Investigator will then submit the DF/HCC AE Reporting form from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events. Outside sites should also provide the Overall Principal Investigator with a copy of any local AE reporting form required to be submitted to their local IRB.

7.5.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

Unless the adverse event meets the definition of serious, the following grade 2 adverse events do not require expedited reporting to the Overall Principal Investigator or the DFCI IRB: nausea; vomiting; fatigue; anemia; anorexia; headache; constipation; and diarrhea.

Unless the adverse event meets the definition of serious, lymphopenia of any grade does not require expedited reporting to the Overall Principal Investigator or the DFCI IRB.

These AEs still must be reported through the routine reporting mechanism (i.e. case report form).

7.6 Expedited Reporting to the Food and Drug Administration (FDA)

The Investigator Brochure (reference safety information for assessment of expectedness of serious

adverse reactions) will be used as the document for the definition of expectedness/listedness for serious adverse events for ceralasertib and Olaparib.

The Overall Principal Investigator, as study sponsor and IND holder, will be responsible for all communications with the FDA. The Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

Specifically, the Overall Principal Investigator will notify the FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the study treatment that is both serious and unexpected. Each written notification shall be made as soon as possible, and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A (MedWatch) or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". Follow-up information to a safety report should be submitted as soon as the relevant information is available.

The Overall Principal Investigator must also notify FDA of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND as soon as possible but in no event later than 7 calendar days after initial receipt of the information. Notification may occur via telephone, facsimile, or other mode of transmission. In the event a 7-day report is required, the Overall Principal Investigator or designee will consult with the assigned FDA Project Manager and follow the preferred mode of communication for reporting the event.

The Overall Principal Investigator will determine whether any AE's reported in an expedited manner on an Expedited AE Reporting form meet criteria for submission as an expedited report to the FDA. The Overall Principal Investigator will prepare the FDA expedited report using information provided by the treating investigator on the Expedited AE Reporting form.

7.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.8 Reporting to AstraZeneca

7.8.1 Serious and Unexpected Adverse Reactions (SUSAR) Reporting to AstraZeneca

The Principal Investigator or designee must inform AstraZeneca at the same time as notifying the FDA, via a MedWatch/AdEERs form, of any serious and unexpected adverse reactions (SUSARs) that occur in accordance with the reporting obligations of 21 CFR 312.32. A copy of the MedWatch/AdEERs report must be provided to AstraZeneca.

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

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

7.8.2 Expedited Reporting to AstraZeneca

The Overall Principal Investigator or his designee will report any of the following events to AstraZeneca in an expedited manner:

- Pregnancy in a female participant who received study treatment (see section 7.6.3)
- Overdose of study treatment (see section 7.8.3)
- Potential Hy's Law (PHL) criteria met for liver injury (see Appendix A)

The initial report must be within 24 hours of PI notification of such events. If only limited information is initially available, a follow-up report is required. All serious adverse events should be followed to resolution or stabilization.

Initial and follow-up safety reports will utilize the DF/HCC AE Reporting form and will be sent electronically to: [REDACTED]

7.8.2.1 Reporting Overdose to AstraZeneca

If an overdose on an AstraZeneca study drug occurs in the course of the study, then it must be reported to AstraZeneca in an expedited manner (see section 7.8.2).

There is currently no specific treatment in the event of overdose with Olaparib and ceralasertib and possible symptoms of overdose are not established. Olaparib and ceralasertib 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. Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca.

7.8.2.2 Reporting Pregnancy to AstraZeneca

Any pregnancy in a female participant treated with study treatment will be reported to AstraZeneca in an expedited manner (see section 7.8.2).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca.

Maternal exposure

If a patient becomes pregnant during the course of the study ceralasertib and Olaparib should be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 1 month *after the last dose* should be followed up and documented. 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. Any adverse events associated with maternal exposure and pregnancy outcomes (eg. congenital abnormalities/birth defects and spontaneous miscarriages) must be reported using SAE reporting guidelines (see section 7.8.1). 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.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose. Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

7.8.2.3 Potential Hy's Law Criteria Met Reporting to AstraZeneca

Any potential Hy's law criteria met (see Appendix A) will be reported to AstraZeneca in an expedited manner (see section 7.8.2).

7.8.3 Additional Reporting to AstraZeneca

Serious adverse events that do not require expedited reporting (see sections 7.8.1 and 7.8.2) will be reported to AstraZeneca by the Overall Principal Investigator or Designee. This information should be reported to AstraZeneca on a monthly basis and under no circumstance less frequently than quarterly. Safety reports will utilize the DF/HCC AE Reporting form and will be sent electronically to:

[REDACTED]

7.9 Reporting to Funding Partner – The Osteosarcoma Institute (OSI):

The Principal Investigator or designee must inform OSI at the same time as notifying the FDA, via a MedWatch/AdEERs form, of any serious and unexpected adverse reactions (SUSARs) that occur in accordance with the reporting obligations of 21 CFR 312.32. A copy of the MedWatch/AdEERs report must be emailed to OSI at [REDACTED] accompanied by a request for an email reply acknowledging receipt, and will be considered delivered when OSI provides such reply. 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 OSI at the same time. The Principal Investigator will report all other SAEs to OSI on a monthly basis. Final summary line-listings of all SAEs notified to regulatory authority and OSI during the Project shall be provided to the OSI at the end of the study.

8. PHARMACEUTICAL AGENT INFORMATION

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9. BIOMARKER CORRELATIVE, AND SPECIAL STUDIES

A key aspect of this trial is integrated correlative studies to define biomarkers of response to DDR inhibitors in osteosarcoma. There are two approaches to defining biomarkers: 1) sequencing to identify genomic events in the DDR pathway and 2) functional assessment of the DDR pathway with immunohistochemistry using antibodies that have correlated with response to PARP plus ATR inhibitor in other diseases (Alan D'Andrea personal communication). Furthermore, patient derived models are extremely valuable in determining biomarkers and for understanding biology. Thus, a second objective of the correlative studies component of the trial is to determine the ability to collect high value specimens in a clinical trial with this design. Finally, circulating tumor DNA has been demonstrated to correlate with therapy response and disease progression in a small number of patients and we will evaluate circulating tumor DNA in this patient population during therapy.

Summary Table of Blood and Tumor Specimen Collection for Biomarker, Correlative and Special Studies

	Pre-Treatment (Cycle 1, Day 1)		Cycle 1 Day 6 (+/- 1 day)	Cycle 2 Day 1	Resection	Tumor Evals	Surgery or Biopsy	Disease progression
Germline blood sample (EDTA)	X							
PK Samples			X					
Cell Free DNA	X			X	X	X	X	X
Tissue submission	X				X		X	

9.1 Pharmacokinetic Study

The goal of the pharmacokinetic study is to assess the relationship between ceralasertib exposure at steady state and relevant selected biomarker(s) in patients receiving the combination of olaparib and ceralasertib.

Sparse PK samples will be collected in all patient from the study according to the PK sampling schedule described below and pharmacokinetic testing for ceralasertib will be triggered if deemed necessary.

9.1.1 Sample Requirements

At each time point in Section 9.1.2, 2 mL of blood is to be collected into a 3.0 mL lavender top plastic Vacutainer tube containing K₂EDTA. For patients with a central catheter, samples may be obtained centrally or peripherally.

9.1.2 Sampling Schedule

Sites are encouraged to utilize a digital timer/stopwatch programmed to operate continuously as a 24-h clock in order to accurately monitor drug administration and sample collection times. The same timer should be allowed to run without interruption until the last blood specimen has been obtained from the

patient. Timer readings should be noted at each blood sample collection time and recorded on the Pharmacokinetic Worksheet in the Manual of Procedures.

The following sampling schedule will be used in Cycle 1:

Day 6 (+/- 1 day):

- Prior to Day 6 dose
- 1 hour (+/- 30 min) after Day 6 dose

In all cases, the exact time the sample was obtained should be recorded on the Pharmacokinetic Worksheet.

The Pharmacokinetic Worksheet in the Manual of Procedures is to be completed in real time by site staff.

9.1.3 Processing Instructions

Immediately after obtaining each sample, tubes are to be inverted 5 times to mix the blood with the anticoagulant. Tubes are to be placed immediately on wet ice until they are centrifuged. Within 30 minutes of collection, samples are to be centrifuged at 1500 x g for 10 minutes at 4°C. Next, a disposable pipette will be used to transfer all of the plasma, without disturbing the blood cells, into one (1) 2.0 mL self-standing polypropylene cryogenic storage vial with external threads. Please label the cryovial with the patient's study ID number, collection date (mm/dd/yyyy) and time (hh:mm-24 hr clock).

No other identifiers should be included on the label. Place the cryovials on crushed dry ice until they can be transferred into an ultralow temperature freezer within 2 hours after collection. Store at $\leq -70^{\circ}\text{C}$ until contacted by the Study Coordinator at Dana-Farber for shipment if the PK analysis is triggered.

9.1.4 Shipping Instructions

Ship samples only when prompted to do so by the Study Coordinator at Dana-Farber.

Place the sample cryovials in a zip lock plastic biohazard bag. Package samples in a seamless styrofoam container. Place the sample bag over at least 3-4 inches of dry ice on the bottom of the container and completely cover with an additional 3-4 inches or more of dry ice. Seal the styrofoam container within a tight-fitting cardboard shipping box.

Insert copies of the Pharmacokinetic Worksheet for each set of samples into a separate zip lock plastic bag placed on top of the styrofoam container before the external shipping box is sealed. Please retain one copy of the worksheet at the study center and send a copy of the worksheet to the Study Coordinator at Dana-Farber.

Send the samples from Monday to Wednesday by FedEx for delivery by 10 a.m. on the following day. Samples should not be shipped on a Thursday or Friday.

Please provide notification of the sample shipment by e-mail to both

██ Include a Copy of the PK Worksheet, tracking number, number of boxes shipped, and reference "DFCI Osteo ceralasertib" in your email.

Please use this FedEx account number [REDACTED] for these shipments and be sure to also provide reference number [REDACTED]

Ship to: Shipping address will be provided in the Manual of Procedures if PK analysis is triggered.

9.1.5 Methodology

The concentration of ceralasertib will be determined by a validated analytical method based upon high performance liquid chromatography with tandem mass spectrometric detection.

Individual patient plasma concentration-time curves will be analyzed by non-compartmental methods using routines supplied in the WinNonlin Professional Version 5.0.1 software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and variables will be calculated according to standard equations

9.1.6 Use of Plasma Samples for Cell-Free DNA Analysis

Plasma samples remaining after pK analysis is complete may be returned to the UCSF to be used in correlative studies as described in Section 9.2.

9.2 Laboratory Correlative Studies

9.2.1 Cell Free DNA

9.2.1.1 Sampling Strategy

Specimen should be collected at the following timepoints:

- Before initiation of each cycle for the first 2 cycles; specimen must be drawn within 5 days of start of cycle
- Before all surgical resections; specimen must be drawn within 5 days of surgery
- Within one week of all tumor evaluations; specimen must be drawn before the start of the subsequent cycle of therapy
- Before biopsy for concern for progression; specimen must be drawn within 5 days of biopsy
- With disease progression

SEE SECTION 9.3 FOR A SUMMARY OF BLOOD VOLUME FOR RESEARCH BLOOD DRAWS

9.2.1.2 Sample Handling Instructions

Streck tubes will be provided at the time of study activation.

Peripheral blood samples should be obtained as follows:

- Blood should be collected in Streck Cell-Free DNA BCT tubes
 - Collect 10 mL of blood
 - Heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, venipuncture is recommended as a first choice collection method. If a Streck CellFree DNA BCT tube immediately follows a heparin tube in the draw order, we recommend collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT.

- Immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.
- **Store and ship at room temperature.** Ship on the same day of sample collection, preferably Monday through Thursday; same business day preferred.

9.2.1.3 Sample Labeling Instructions

Tubes must be labeled with the patient's study ID number and initials, study time point, and collection date.

9.2.1.4 Sample Shipment

Specimen should be shipped by FedEx Priority Overnight at room temperature for immediate separation, extraction, and storage of plasma and cellular DNA. Samples should be shipped at room temperature from Monday through Thursday for Tuesday through Friday delivery. If blood is collected in the Streck tube on Friday or over the weekend or on the day before a holiday, the sample can be stored at room temperature until shipped on the next business day.

A Specimen Transmittal form (found in the Manual of Procedures) must be included with each shipment. The time point listed on the transmittal form must be written on the transmittal form exactly as outlined in the Manual of Procedures.

Please provide notification of the sample shipment by e-mail to the following study personnel:

- [REDACTED]

Include a copy of the ctDNA Worksheet, tracking number, number of boxes shipped, and reference "DFCI Osteo ceralasertib" in your email.

Please use this FedEx account number [REDACTED] for these shipments and be sure to also provide reference number [REDACTED]

Ship specimens to the following address:

[REDACTED]

9.2.1.5 Methodology

Cell-free DNA will be extracted from plasma samples using the QIAamp Circulating Nucleic Acid Kit (Qiagen). Library preparation with custom barcoded adapters will be completed using the KAPA Hyper Prep kit (Kapa Biosystems). These libraries will undergo hybrid-capture, followed by next-generation sequencing to detect, quantify, and profile translocations and copy number changes for each sample. Relevant translocation partners in the assay include TP53 and ATRX.

9.2.2 Tumor sequencing and immunohistochemistry assessing the DDR pathway

9.2.2.1 Sampling Strategy

Peripheral blood to be submitted at time of enrollment:

- Collect 5ml of blood in EDTA tube when the patient's WBC is estimated to be >1K/ul.

SEE SECTION 9.3 FOR A SUMMARY OF BLOOD VOLUME FOR RESEARCH BLOOD DRAWS

Required tumor biospecimen to be submitted at the **time of enrollment for all patients**:

- Submit tumor tissue from diagnosis and/or the most recent recurrence for which there was a biopsy or surgery performed. Prefer submission of tumor from both time points. If tumor from both time points is available but only one time point will be submitted, prefer most recent recurrence.
- Tissue from local control resection is not acceptable
- Tissue submitted for this study need to be from material that has NOT been decalcified utilizing an acid-based decalcification method (EDTA decalcification acceptable)
- Formalin fixed paraffin embedded (FFPE) tumor block, 15 scrolls of 4-5 micron thick unstained tissue sections along with one unstained slide **or** 20 slides of 4-5 micron thick unstained tissue sections.

OR

- 25 mg or 0.25 cm³ flash frozen tumor from original diagnostic tumor sample, recurrent tumor or, preferably both.

OR

- FFPE block or unstained slides from cytology of fluid with malignant cells such as malignant pleural effusion accepted.

OR

- Other specimens expected to result in adequate DNA quantity and quality for sequencing may substitute for tissue above
 - PI or study staff approval required prior to submission

Required Tumor biospecimen to be submitted at the **time of any biopsy or surgery for patients on protocol therapy**:

- Tissue submitted for this study need to be from material that has NOT been decalcified utilizing an acid-based decalcification method (EDTA decalcification acceptable)
- Formalin fixed paraffin embedded (FFPE) tumor block, 15 scrolls of 4-5 micron thick unstained tissue sections along with one unstained slide **or** 15 slides of 4-5 micron thick unstained tissue sections.

AND

- If available, 25 mg or 0.25 cm³ flash frozen tumor

OR

- Other specimens expected to result in adequate DNA quantity and quality for sequencing may substitute for tissue above
 - PI or study staff approval required prior to submission

Optional tumor biospecimen to be submitted at the time of any biopsy or surgery for patients on protocol therapy:

- **Tumor tissue for patient derived models:**
- 3-4 pieces of fresh tumor (approximately 2-3 mm³ in size) placed in 1 mL of 90% FBS, 10% DMSO in a cryovial.

- Process by cryopreserving sample by freezing slowly to -80 °C while tube is insulated in Styrofoam or other appropriate freezing chamber. Store at -80 °C for at least 12 hours to allow for slow freeze. Do not thaw once at -80. Keep on dry ice for transport.

Optional tumor biospecimen to be submitted at the time of any surgery or biopsy when protocol therapy is complete and patients is within the 2 year follow up period:

- Tumor tissue removed at the time surgery or biopsy performed while patient is on study (patients does not need to still be on protocol therapy).
- Tissue submitted for this study need to be from material that has NOT been decalcified utilizing an acid-based decalcification method (EDTA decalcification acceptable)
- Formalin fixed paraffin embedded (FFPE) tumor block, 15 scrolls of 4-5 micron thick unstained tissue sections along with one unstained slide **or** 15 slides of 4-5 micron thick unstained tissue sections.

AND

- If available, 25 mg or 0.25 cm³ flash frozen tumor

OR

- Other specimens expected to result in adequate DNA quantity and quality for sequencing may substitute for tissue above
 - PI or study staff approval required prior to submission

AND

- **Tumor tissue for patient derived models:**
- 3-4 pieces of fresh tumor (approximately 2-3 mm³ in size) placed in 1 mL of 90% FBS, 10% DMSO
- Process by cryopreserving sample by freezing slowly to -80 °C while tube is insulated in Styrofoam or other appropriate freezing chamber. Store at -80 °C. Avoid freeze/thaw cycles. Keep on dry ice for transport.

SEE SECTION 9.4 FOR A SUMMARY OF TUMOR TISSUE SUBMISSION

9.2.2.2 Sample Handling Instructions

Tumor Tissue:

- FFPE tumor or cytology samples: Slides should be placed in plastic slide containers. Scrolls should be placed in tubes.
- Frozen tumor: Store at -80; keep on dry ice for transport
- Fresh tumor for PDX frozen in FBS and DMSO: Store at -80; keep on dry ice for transport

Peripheral Blood:

- Store at 4°C until sample is shipped.

9.2.2.3 Sample Labeling Instructions

Tumor Tissue:

- Label with patient initials, patient study ID number, and specimen ID (Surgical-Path ID) number. Submit with redacted pathology report from the same case from which the sample was obtained and a sample submission form (see Manual of Procedures).

Peripheral Blood:

- Label with patient initials, patient study ID number, and date collected. Submit with a sample submission form (see Manual of Procedures).

9.2.2.4 Sample Shipment

Tumor Tissue:

- FFPE tumor or cytology samples: Ship in plastic slide containers or tubes (for scrolls) at room temperature by overnight shipping. NOTE package slides carefully with adequate padding to prevent breakage in transit. Samples should be shipped from Monday through Thursday for Tuesday through Friday delivery.
- Frozen tumor and fresh tumor for PDX in FBS and DMSO: Ship on dry ice by overnight shipping. NOTE be sure to pack in adequate dry ice to prevent thawing during shipment. Samples should be shipped from Monday through Thursday for Tuesday through Friday delivery.

Peripheral blood:

- Ship cold, but not frozen, with a cold pack. Samples should be shipped from Monday through Thursday for Tuesday through Friday delivery.

A Specimen Transmittal form (manual of procedures) and redacted pathology report must be included with each shipment.

Please provide notification of the sample shipment by e-mail to the following study personnel:

- [REDACTED]

Include a copy of the Tissue Biomarker Worksheet and/or Peripheral Blood Worksheet, tracking number, number of boxes shipped, and reference “DFCI Osteo ceralasertib” in your email.

Please use this FedEx account number [REDACTED] for these shipments and be sure to also provide reference number [REDACTED]

Ship specimens to the following address:

[REDACTED]

9.2.2.5 Methodology

DNA will be extracted from tumor tissue using the AllPrep kit (Qiagen). Germline DNA will be extracted from peripheral blood using the DNeasy Blood and Tissue kit (Qiagen). Libraries will be made using the TruSeq Nano kit (Illumina) and sequenced to a depth of 30X for germline and 60X for tumor, allowing for detection of mutations, copy number changes, and translocations.

Tumor tissue will be examined by immunohistochemistry to assess the DDR pathway. Antibodies against ATM, P-ATM, H2AX, γ H2AX, Chk2, and P-Chk2 will be used.

Tumor samples preserved in FBS/DMSO will be banked for future implantation into immunodeficient

NSG mice.

9.3 Summary of Blood Volumes for Research Blood Draws:

10 mL of blood in Streck CellFree DNA BCT tube at each of the following timepoints:

- Before initiation of each cycle for the first 2 cycles
- Before all surgical resections
- Within one week of all tumor evaluations
- Before biopsy for concern for progression
- With disease progression

5 mL of blood, collected in EDTA for germline analysis at enrollment.

2 mL of blood is to be collected into a 3.0 mL lavender top plastic Vacutainer tube containing K₂EDTA at each of the following timepoints:

- Prior to Cycle 1, Day 6 dose
- 1 hour after Cycle 1, Day 6 dose

9.4 Summary of Tumor Tissue Submission

At time of enrollment for patients in cohort 1 and 2 (required):

From diagnosis and/or most recent recurrence: FFPE from non-decalcified specimen OR frozen OR alternative expecting to yield sufficient DNA (after approval from PI)

At time of any surgery or biopsy performed on study; patient does not need to be on protocol therapy (encouraged):

FFPE from non-decalcified specimen AND frozen OR alternative expecting to yield sufficient DNA (after approval from PI)

3-4 pieces of fresh tumor (approximately 2-3 mm³ in size) placed in 1 mL of 90% FBS, 10% DMSO and slowly frozen to -80 °C (optional)

10. STUDY CALENDAR

Baseline laboratory tests and screening studies must be completed within 14 days prior to the date of registration. Laboratory tests used to meet eligibility requirements may be completed within 14 days prior to date of registration, but must be repeated prior to Cycle 1, Day 1 if obtained > 7 days prior to Cycle 1, Day 1. Baseline disease assessments, such as MRIs, CT scans and nuclear medicine studies, must be performed within 14 days of the date of registration. Protocol therapy must be initiated within 5 days of registration.

Once enrolled, required observations should be obtained within $\pm$ 3 days of the protocol-specified timeframe, unless otherwise noted. Start of subsequent cycles may be delayed by up to 3 days for logistical reasons without being considered a protocol violation.

Observation	Baseline	C1, D1	C1, D6	C1, D15	C2- 4, D1	C5+, D1	End of Therapy	Surgery or biopsy ¹²
-------------	----------	-----------	-----------	------------	--------------	------------	-------------------	---------------------------------------

History	X	X			X	X	X	
Physical Examination and AE assessment (including vital signs)	X	X			X	X	X	
Performance status	X							
Tumor and germline sequencing report, if available	X							
Baseline tumor specimen ¹	X							
Baseline blood sample for sequencing		X						
ECHO	X							
EKG performed in triplicate	X							
Laboratories ²	X	X	X	X	X	X	X	
Serum or Urine Pregnancy Test	X				X	X	X	
Pharmacokinetics			X					
Tumor Imaging ³	X				X ⁴	X ⁴	X ⁴	
Chest CT	X				X ⁴	X ⁴	X ⁴	
Bone Scan / PET Scan ⁵	X						X (Optional)	
ctDNA study sample ⁶		X			X	X	X	X
Tumor Sample ¹								X
Surgical Pathology Report (redacted)								X

OBTAIN OTHER STUDIES AS NEEDED FOR GOOD PATIENT CARE.

C = cycle

D = day

¹ See Section 9.2 for tumor specimen requirements

² CBC with differential, glucose, sodium, potassium, calcium, magnesium, BUN, Creatinine, Total bilirubin, ALT, AST, GGT, LDH. PTT and INR only obtained at baseline and as clinically indicated. See Section 5.2 for details. Urinalysis only at baseline and if clinically indicated.

³ Evaluations should include CT or MRI of all lesions meeting eligibility criteria. Use the same imaging modality for all disease evaluations. For lung metastases, chest CT is recommended. For soft tissue lesions, CT or MRI may be used.

- Imaging studies when required per protocol must be obtained within 7 days of Day 1 (See Section 5.2.2 for details).
- Participants who have a RECIST 1.1 response (CR or PR) on any evaluation following Cycle 4 will have confirmatory imaging 4 weeks after the evaluation upon which the RECIST 1.1 response was detected (additional imaging time point)
- For participants who undergo a surgical resection following Cycle 4, either a CT scan or MRI post-surgery to establish a new baseline is strongly recommended before re-initiating study treatment.

⁴ Before odd numbered cycles (3, 5, 7, etc.) for the first 12 months and then every 3 cycles thereafter.

⁵ Bone scan or PET scan is required at screening and Bone scan or PET scan is optional to the treating physician, at the end of therapy. Also permitted when clinically indicated.

⁶ At enrollment, before initiation of the first two cycles, before each tumor evaluation (within 5 days), at the time of any surgery or biopsy on study and at progression. See Section 9.2.1.1.

End of Therapy: End of Therapy visit should occur within 30 days inclusive from the date the patient is taken off of protocol therapy.

Follow-up: After participants meet off-protocol therapy criteria and complete the end of therapy observations in the above table, they will enter follow-up. Participants will remain in follow-up until two years from last dose of study treatment or death, whichever occurs first. During follow-up, participants will undergo disease

evaluations according to a schedule determined by their treating physician. Disease and vital status will be collected every 6 months during the follow-up period.

11. MEASUREMENT OF EFFECT

For the purposes of this study, participants should be re-evaluated according to the schedule outlined in Section 10. Confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

11.1 Definitions

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that relapse or progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Event-Free Survival: Event-Free Survival (EFS) is defined as the time from registration to the earlier of progression, relapse, or death due to any cause. Participants alive without disease progression or relapse are censored at date of last disease evaluation.

Overall Survival: Overall survival (OS) is defined as the time from registration until death from any cause. Participants who are alive will be censored on the date of last contact.

11.2 Antitumor Effect

Response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

11.2.1 Definitions

11.2.1.1 Measurable disease. For lesions other than lymph nodes, measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness

recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

11.2.1.2 Non-measurable evaluable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and cystic lesions are all considered non-measurable (except as described in Section 11.3.1.3). Bone lesions are considered non-measurable unless associated with a soft tissue lesion that itself meets criteria for measurable disease.

11.2.1.3 Important notes

Tumor lesions that are situated in a previously irradiated area are not considered measurable or evaluable unless that site meets criteria for progression after completion of radiation.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) unless biopsy proven since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases, particularly if biopsy proven, can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

11.2.2 Requirements for Disease Assessments

Investigators are to determine the optimal mode of disease assessment at baseline, including anatomic imaging studies, nuclear medicine studies, clinical measurements, tumor markers, and bone marrow biopsies. 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 is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before registration.

11.2.3 Response Criteria

11.2.3.1 Evaluation of Target Lesions

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph

nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2.3.2 Evaluation of Non-Target Lesions

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.2.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the

initial scan on which the lesion was discovered.

11.2.3.4 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 wks Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

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.

11.3 Response Review

Participants with confirmed objective response (partial response or better) will have de-identified imaging studies submitted to the Study Coordinator for central confirmation of response. Imaging studies to be submitted include baseline scans, initial scans documenting response, and second set of scans confirming response. When relevant to the patient’s response assessment, de-identified copies of bone marrow pathology reports and tumor marker lab reports will be submitted as well.

12. DATA REPORTING/REGULATORY REQUIREMENTS

12.1 Data Reporting

12.1.1 Method for Data Submission

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.1.3 Timelines for Data Submission

All investigative sites are expected to submit data in InForm according to the following timelines.

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Form	Within 14 days of registration
Adverse Event Report Form (Baseline Adverse events)	Within 14 days of registration
Baseline Disease Assessment Form	Within 14 days of registration
Reporting Period 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 cycles in which disease evaluated
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
30-Day Follow up Form	Within 14 days of the protocol defined follow up visit date

12.1.4 Submission of Source Documentation and Imaging Studies

Aside from submission of data in InForm, investigative sites are expected to submit to the Overall PI at Dana-Farber the source materials listed in Section 4.3 and de-identified imaging studies that meet criteria given in Section 11.3.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. 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 Overall PI and study team.

The DSMC will review this protocol up to four times a year 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; toxicity information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention; any response information; audit results; safety report from the interim analysis and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

The Principal Investigator or designee will have regular calls (approximately monthly) with AstraZeneca to review the toxicity data for participants enrolled on the study, particularly participants who are less than 18 years old.

12.3 Multicenter Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Design

This is a single arm, multi-center, phase II, open-label clinical trial to evaluate the clinical activity of Olaparib in combination with ceralasertib in Participants with recurrent osteosarcoma. The vast majority of participants with recurrent osteosarcoma are adolescents and young adults (median age at diagnosis 15 years). As such, enrollment will be restricted to participants between 12 and 40 years of age. Participants will receive twice daily dosing of oral olaparib on days 1-28 and daily oral ceralasertib on days 1-7. Participants can remain on treatment for up to 2 years if progression has not occurred. A Simon's two-stage design will be used to evaluate the primary objective within Cohort 1 regarding the efficacy of the combination therapy.

After enrollment of 4 patients in Cohort 1, the study was amended (with v4) to use a different dosing schedule. The first 4 patients will contribute to a descriptive analysis, but will not be used in the Simon's two stage design of the primary endpoint. However, the original total sample size of up to 43 Cohort 1 patients was not changed; as a result, the Simon's two stage design was amended for a smaller sample size, but preserving similar operating characteristics.

13.1.2 Endpoints

For Cohort 1, the primary endpoint is a patient's disease status at completion of 4 cycles of therapy, about 16 weeks after enrollment (a binary endpoint). This endpoint was chosen in contrast to tumor shrinkage due to the fact that the tumor stroma for osteosarcoma consists of a calcified matrix, and radiologic tumor shrinkage does not always correlate with histologic response (which is often more favorable).

For each patient, it will be determined whether: a) an 'event' has occurred prior to or at the disease evaluation after 4 cycles (roughly 4 months after enrollment); or, b) no event prior to or at the disease evaluation after 4 cycles. An event is defined as the occurrence of relapse, disease progression as defined by RECIST 1.1, or death from any cause. The primary endpoint, "4-months event-free", is binary (1=event at or before 4 cycles; 0=no event at or before 4 cycles). Baseline assessments will be obtained prior to first administration of the study drug. Disease assessments will occur every 8 weeks. If for any reason a patient does not complete the disease evaluation after 4 cycles (due to withdrawal from the study, lost to follow-up, or other reason), the patient will be counted as having an event for the purposes of the two-stage analysis of the primary objective. This is expected to be a rare occurrence.

For Cohort 2, the primary endpoint will be the submission of paired pre- and post-treatment tumor samples for correlative studies.

The endpoint for Secondary Objective 1 is a patient's best overall objective response (assessed per RECIST 1.1). For Secondary Objective 2, the endpoints are event-free survival (EFS) and overall survival (OS), as defined in section 11.1.

The endpoint for Secondary Objective 3 (Cohort 2 only), is a patient's disease status after the evaluation which occurs approximately 12 months after enrollment (a binary endpoint). For each patient, it will be determined whether: a) an 'event' has occurred prior to or at the ~12-month disease evaluation; or, b) no event at or before the ~12-month disease evaluation. An event is defined as the occurrence of relapse, disease progression as defined by RECIST 1.1, or death from any cause. This endpoint, "12-months event-free", is binary (1=event at or before ~12 months; 0=no event at or before ~12 months).

The endpoint for Secondary Objective 4 is the occurrence of a toxicity, as graded according to CTC Version 4.0.

For Exploratory Objective 1, the pharmacokinetic data will be analysed if triggered using a population PK approach. Parameters will be calculated, such as :

$C_{\max}$	The peak plasma concentration of a drug after administration.
$t_{\max}$	Time to reach $C_{\max}$.
$C_{\min}$	The lowest (trough) concentration that a drug reaches before the next dose is administered.
Area under the curve (AUC)	The integral of the concentration-time curve (after a single dose or in steady state).

For Exploratory Objectives 2 and 3, the endpoint is a patient's best overall objective response (assessed per RECIST 1.1). We will assess gene alterations in the DNA damage response pathway and other biomarkers of DNA damage response in pre-treatment patient samples. We will evaluate a quantitative cell-free DNA assay as a surrogate marker for patient response.

13.2 Sample Size, Accrual Rate, Study Duration and Evaluability

Total accrual: Up to approximately 63 patients (43 Cohort 1, [39 at the new dose level, 4 at the original dose level], 20 Cohort 2)

Accrual goal: 34 evaluable Cohort 1 patients (participants who are inevaluable will be replaced).

The sample size is driven by the requirement of 34 evaluable patients for the Simon's two-stage design to address the Primary Objective for Cohort 1. Assuming that about up to 10% of Cohort 1 patients could be inevaluable, up to approximately 39 Cohort 1 patients could be enrolled to obtain 34 evaluable Cohort 1 patients. At an accrual rate of 1.5-1.8 Cohort 1 patients per month, Cohort 1 enrollment will be completed in approximately 24 months. Enrollment into Cohort 2 will continue for as long as Cohort 1 enrollment is ongoing, and then the study will be closed to further accrual. At an accrual rate of 8-10 Cohort 2 patients per year, the estimated total accrual to Cohort 2 will be approximately 20 patients.

Study duration: If the last patient enrolled is treated for 2 years, then the total study duration will be approximately 4 years with the primary outcome measure being available approximately 28 months after the first patient is enrolled.

Evaluability: Evaluability is defined in two ways, one for the primary objective (Cohort 1) and another for the secondary objective (Cohorts 1 and 2).

- a) In Cohort 1, to be evaluable to address the study's primary objective, i.e., to be included in the Simon's two-stage design, a patient must be eligible and have received at least one dose of protocol therapy, olaparib and ceralasertib at the dose level instituted with protocol version 4. Participants who enrolled on the trial, but do not received one dose of both olaparib and ceralasertib or who receive the initial dose level (prior to protocol version 4) will be deemed inevaluable and will be replaced in the enrollment count of participants required to address the study's primary objective.
- b) To be evaluable for the study's secondary objective regarding the assessment of best overall response per RECIST 1.1, i) participants must be eligible; ii) participants must have received at least one dose of protocol therapy with olaparib and ceralasertib at the dose level instituted with protocol version 4; and, iii) for the subgroup of participants who achieved a CR or PR at the pre-Cycle 5 evaluation, there must be confirmation of that response on imaging at least 4 weeks later and prior to surgery. However, if such a patient has surgery without confirmation of the CR/PR, then the patient will be deemed inevaluable for the study's secondary objective regarding the assessment of best overall response per RECIST 1.1.

13.3 Stratification Factors

For descriptive purposes, and to identify subgroups to be included in particular study objectives, patients will be stratified into two cohorts:

Cohort 1 - patients with unresectable disease; and,

Cohort 2 - patients with resectable disease limited to the lungs.

13.4 Interim Monitoring Plan

We will perform interim monitoring for the primary endpoint, "event-free at 4 months" by applying a Simon's two-stage design to the evaluable patients in Cohort 1. Accrual will be suspended at the end of stage 1 until the minimum number of participants who are 4-months event-free have been identified, to justify proceeding to stage 2.

Toxicity will be monitored on an ongoing basis. In addition to interim monitoring for the primary endpoint, safety and tolerability will be also assessed at the end of stage 1. A report of the toxicity findings at this time will be communicated to the DSMC.

13.5 Analysis of Primary Endpoints

Primary Objective 1: To address Primary Objective 1 for Cohort 1, a Simon's two-stage design will be applied to the primary (binary) endpoint, event-free at 4-months.

Stage 1 – Enroll 15 evaluable patients. If 1 or fewer participants are 4-months event-free, the trial will be terminated because the combination of olaparib and ceralasertib is not associated with sufficient evidence of activity for further investigation. If 2 or more participants are 4-months event-free, then enrollment will be continued to Stage 2.

Stage 2 – Enroll an additional 19 evaluable participants, for a total of 34. If 9 or fewer participants are 4-months event-free, the trial will be terminated because the combination of olaparib and ceralasertib is not associated with sufficient evidence of activity for further investigation. If 10 or more participants are 4-months event-free, then we will conclude that there is sufficient activity for further investigation of the combination therapy.

Accrual will be temporarily halted for the assessment of the 4-month event-free status of patients in Stage

1. However, if at any time during the accrual to Stage 1, 2 or more Stage 1 participants are identified as 4-months event-free, accrual will be permitted to continue to Stage 2 without stopping.

The operating characteristics of this design are as follows: 90% power to detect a 20% difference (19% as poor [null hypothesis], versus 39% [alternative hypothesis] as sufficiently good) in the proportion who are event-free at 4-months, with a type 1 error of 0.09. This design has an expected sample size of 30.36 and a probability of early termination of 0.192.

The null hypothesis of 19% was chosen based on the results of 96 patients enrolled on four phase 2 trials conducted by the Children's Oncology Group (COG) where the event-free rate at 4 months is 12% {95% CI: 6.0%-19%}⁷. Also, in these findings, 40% was considered a successful disease control rate, thus the selection of 39% as the alternative.

In addition, we will calculate the proportion who are event-free at 4 months, as the total number event-free at 4-months divided by the number of evaluable patients and place an exact two-sided 95% confidence interval on this proportion. This calculation will be performed separately for the two dose levels of evaluable Cohort 1 patients, i.e., within the first four evaluable Cohort 1 patients at the original dose level/schedule, and then in the balance of Cohort 1 who received the amended dose level/schedule.

Primary Objective 2 – We will estimate the proportion of patients who have paired pre-/post-treatment tumor samples adequate for biomarker studies and / or derivation of PDX models and place an exact two-sided 95% confidence interval on the proportion.

13.6 Analysis of Secondary Efficacy Endpoints

Secondary Objective 1 – We will estimate the objective response rate in participants with relapsed osteosarcoma treated with olaparib in combination with ADZ6738. The response rate will be calculated as the number of patients with CR or PR divided by the number of evaluable patients. A 95% confidence interval will be placed on the response rate. This analysis will be performed separately within Cohorts 1 and 2.

Secondary Objective 2 – Kaplan-Meier curves of EFS and OS will be generated, using standard errors according to the methods of Greenwood, separately for Cohort 1 and Cohort 2. A point-estimate of 4-month EFS will be presented with an exact two-sided 95% confidence interval.

Secondary Objective 3 – Within Cohort 2, we will calculate the proportion who are event-free at 12-months, as the total number event-free at 12-months divided by the number of evaluable patients and place an exact two-sided 95% confidence interval on this proportion.

Secondary Objective 6 – The number and proportion of adverse events will be tabulated by type and grade. This analysis will be performed overall and separately for Cohort 1 and 2. Within a given patient, a given adverse event will be counted only once at the highest grade. Listings of all the adverse events will be generated.

13.7 Analysis of Exploratory Endpoints

Exploratory Objective 1 - The pharmacokinetic endpoints listed above will be calculated if deemed necessary. Appropriate measures of variability, such as the mean and standard deviation, quartiles, minimum, and maximum, will be calculated.

For Exploratory Objective 2, we will descriptively tabulate the number and percentage of types of gene alterations in the DNA damage response pathway and other biomarkers of DNA damage in pre-treatment patient samples. In a purely exploratory fashion, we will use a Fisher's exact test to test for association of the occurrence of particular gene alterations and biomarkers versus response (SD, <SD), within Cohort 1, within Cohort 2, and overall.

For Exploratory Objective 3, we will generate box and whisker plots of quantitative cell-free DNA by response (<PR, ≥PR) and perform a Wilcoxon rank-sum test of the quantity of cell-free DNA versus response.

14. PUBLICATION PLAN

The results are expected to be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported. The initial release may be an abstract to be presented at a relevant scientific meeting. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

- **Introduction**

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

The Investigator participates, together with Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

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

- **Definitions**

- **Potential Hy's Law (PHL)**

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

- **Hy's Law (HL)**

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

- **Identification of Potential Hy's Law Cases**

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

- ALT $\geq 3 \times$ ULN
- AST $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ ULN

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

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

- **Follow-up**

- **Potential Hy's Law Criteria not met**

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

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

- **Potential Hy's Law Criteria met**

If the patient does meet PHL criteria the Investigator will:

- Notify the Company

Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

The Company contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Company.
- Complete the three Liver CRF Modules as information becomes available
- **Review and Assessment of Potential Hy's Law Cases**

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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Company contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The Sponsor Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly

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

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

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law Case') ensuring causality assessment is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the previously submitted PHL SAE report following CSP process for SAE reporting according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined

Actions Required for Repeat Episodes of Potential Hy's Law

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

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

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease,

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition# compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Appendix

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

References

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

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

APPENDIX B PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria

Karnofsky and Lansky performance scores are intended to be multiples of 10

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	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.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX C LIST OF STUDY SITES

Dana-Farber/Boston Children's (Dana-Farber Pediatrics)

University of California San Francisco

Memorial Sloan Kettering Cancer Center

MD Anderson Cancer Center

APPENDIX D DRUG ADMINISTRATION DIARY

Please see separate Drug Diary Document.

APPENDIX E GUIDELINES REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

Ceralasertib is an investigational drug for which no data on *in vivo* interactions are currently available. Potential interaction is considered on the basis of preclinical *in vitro* data only.

The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in this appendix. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with ceralasertib is safe. If ceralasertib is being administered in combination, potential interactions of the combination partner should also be considered.

Restrictions regarding drugs affection CYP3A metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and ceralasertib; a potential interaction is considered on the basis of preclinical and *in vitro* data only. ceralasertib is predominantly eliminated via CYP3A metabolism (approximately 60%), therefore CYP3A inhibitors or inducers may increase or decrease exposure to ceralasertib, respectively. Potent inhibitors or inducers of CYP3A should not be combined with ceralasertib.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP3A activity. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

Table 1: Drugs Known to be Inhibitors and inducers of CYP3A

Potent CYP3A inhibitors	Potent CYP3A inducers
boceprevir	avasimibe
clarithromycin	carbamazepine
conivaptan	enzalutamide
elvitegravir/ RIT	mitotane
fluconazole	phenobarbital
grapefruit juice ^{ac}	phenytoin
indinavir	rifabutin
itraconazole	rifampin
ketoconazole	St John's Wort
lopinavir/ RIT	
mibefradil	
nefazodone	
nelfinavir	
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
tipranavir/RIT	
troleandomycin	
voriconazole	
List created using the University of Washington Drug-Drug Interaction Database January 2013. RIT = Ritonivir.	

Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity

a. Double-strength grapefruit juice

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

Drugs known to be inhibitors or inducers of Pgp and/or BCRP, undertake appropriate monitoring if coadministration is necessary.

Ceralasertib is a substrate of Pgp and BCRP. Co-administration of Pgp inhibitors/inducers or BCRP inhibitors/inducers may affect exposure to Ceralasertib therefore it is recommended that these are not co-administered with Ceralasertib.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate Pgp activity or BCRP activity. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with Ceralasertib.

Table 2: Drugs known to be inhibitors or inducers of P-gp

Drugs Known to be Inhibitors of Pgp^a	Drugs Known to be Inducers of Pgp^b
Amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cremophor curcumin diltiazem dronedarone elacridar erythromycin felodipine fluvoxamine ginkgo indinavir itraconazole ketoconazole lapatinib lopinavir and ritonavir mibefradil milk thistle mirabegron nelfinavir nifedipine nitrendipine paroxetine quercetin quinidine	avasimibe carbamazepine efavirenz genistein phenytoin rifampin St Johns Wort

ranolazine rifampin ritonavir saquinavir/ritonavir schisandra chinensis extract St Johns Wort talinolol telaprevir telmisartan ticagrelor tipranavir/ritonavir tolvaptan valspodar (PSC 833) verapamil	
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a. Inhibitors listed for P-gp are those that showed >25% increase in exposure to a P-gp substrate (e.g. digoxin).

b. Inducers listed for Pgp are those that showed >20 % decrease in exposure to a P-gp substrate (e.g. digoxin)

Table 3: Drugs known to be inhibitors or inducers of BCRP

Drugs Known to be Inhibitors of BCRP	Drugs Known to be inducers of BCRP
Afatinib Aripiprazole Curcumin Cyclosporine Elacridar Erlotinib Fluvastatin Fumitremorgin Gefitinib Ivermectin Lapatinib Nilotinib Novobiocin Pantoprazole Pitavastatin Ponatinib Quercetin Quizartinib Rabeprazole Regorafenib Rilpivirine Sulfasalazine Sunitinib Tacrolimus Teriflunomide Trametinib Trifluoperazine Vismodegib eltrombopag Atazanavir Lopinavir Ritonavir	Please check individual drugs on a case by case basis

Tipranavir Omeprazole Estrone 17b-estradiol Imatinib mesylate	
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List created using <http://dmd.aspetjournals.org/content/dmd/43/4/490.full.pdf>

Note: Although BCRP is involved in a number of clinically relevant DDIs, none of the cited inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYP3A4 and/or CYP2B6, undertake appropriate monitoring if coadministration is necessary.

Ceralasertib is a potential inducer of CYP3A4 and CYP2B6. Therefore caution should be applied with co administration of drugs that are either completely metabolised by CYP3A4 and/or CYP2B6, or that are substrates of CYP3A4 and/or CYP2B6 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP3A4 and/or CYP2B6 may be reduced.

Table 4: Drugs known to be metabolised by CYP3A4 and have a narrow therapeutic index

Alfentanil Cyclosporine Dihydroergotamine Ergotamine Fentanyl Pimozide Quinidine Sirolimus Tacrolimus Astemizole Cisapride Terfenadine

Table 5 : Drugs known to be metabolised by CYP2B6 and have a narrow therapeutic index

Cyclophosphamide Ifosfamide Efavirenz Bupropion Propofol Thiotepa Sorafenib alfentanil ketamine methadone methoxetamine nevirapine propofol selegiline sertraline sorafenib tamoxifen valproic acid
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From Flockhart DA (2007). "Drug Interactions: Cytochrome P450 Drug Interaction Table". Indiana University School of Medicine

Drugs known to be substrates of OATP1B1 and BCRP, undertake appropriate monitoring if coadministration is necessary

Ceralasertib is also an inhibitor of OATP1B1 and BCRP. Caution should be applied with coadministration of substrates of OATP1B1 and/or BCRP as ceralasertib may increase their exposure. These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with ceralasertib.

Table 6: Drugs known to be substrates of OATP1B1

Atorvastatin
Fluvastatin
Lovastatin
Pitavastatin
Pravastatin
Rosuvastatin
Simvastatin
Ezemibe
Simvastatin
Methotrexate
Rifampin
Bosentan
Glyburide
Repaglinide
Valsartan
Olmesartan
Atrasentan

List created using <https://www.solvobiotech.com/transporters/OATP1B1>

Table 7: Drugs known to be substrates of BCRP

Anthracyclines
Daunorubicin
Doxorubicin
Topotecan
SN-38
Irinotecan
Methotrexate
Imatinib
Irinotecan
Mitoxantrone
nucleoside analogs
prazosin
pantoprazole
topotecan
rosuvastatin and other statins
teriflunomide
chlorothiazide

List created using <https://www.solvobiotech.com/transporters/bcrp>

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APPENDIX F

**Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan**

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Policies and Operations..

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions.
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.
- Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.

- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- ***Protocol revisions:*** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.
- ***Protocol closures and temporary holds:*** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3 IRB Re-Approval

Verification of IRB re-approval for the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received for the External Site on or before the anniversary of the previous approval date.

3.4. DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5. Participant Registration

Participation Registration is outlined in section 4.4 of the protocol document.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.3.1 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

3.3.2 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.5. Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web based training for all eCRF users.

3.5.1. Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the External Sites will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

3.6. Protocol Reporting Requirements

3.6.1. Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

3.6.2. Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

3.6.3. Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.4. Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

On-Site Monitoring: On-site monitoring will occur at least once per site. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents,

pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled.

Virtual Remote Monitoring: Virtual monitoring will occur on a regular basis, approximately every 6 months. The Coordinating Center will request source documentation from participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

4.5. Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.6. Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

5. AUDITING: QUALITY ASSURANCE

5.4. DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.5. Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.6. Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the IRB as applicable.

5.7. External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.