Study Title:	A Phase II, Open-Label, Study of Olaparib in combination with either Durvalumab (MEDI4736), Selumetinib or Capivasertib, or Ceralasertib monotherapy in Patients with Metastatic Triple-Negative Breast Cancer
Protocol Number:	18504
ClinicalTrials.gov ID:	NCT03801369
Investigational product:	Olaparib, Durvalumab, Selumetinib, Capivasertib, Ceralasertib
Version Number:	9.2
Version Date:	10 Apr 2023
Replaces:	9.1
Principal Investigator:	**Alexandra Zimmer, MD, MSc**
	Division of Hematology and Medical Oncology Oregon Health & Science University 3181 SW Sam Jackson Park Road, OC14HO Portland, OR 97239 Phone: 503-494-6594 Email: hobbev@ohsu.edu
Co-Investigator(s):	**Janelle Meyer, MD** Oregon Oncology Specialists 875 Oak Street, Suite 4030 Salem, OR 97301-3984 Phone: 503-561-6444 Email: jmeyer@orcancer.com **Jennifer Specht, MD** Seattle Cancer Care Alliance 825 Eastlake Ave E, G3630 Seattle, WA 98109-1023 Phone: 206-606-2053 Email: jspecht@uw.edu **Douglas Yee, MD** Masonic Cancer Center, University of Minnesota 420 Delaware Street SE MMC 806 Minneapolis, MN 55455 Phone: 612-626-8487 Email: yeexx006@umn.edu **Ben Ho Park, MD PhD** Vanderbilt University Medical Center 2220 Pierce Avenue, Preston Research Building, Rm 770 Nashville, TN 37232 Phone: 615-936-1919 Email: ben.h.park@vumc.org
Statistician:	**Lim, Jeong Youn, PhD** Biostatistics Shared Resource, Knight Cancer Institute Oregon Health & Science University 2730 SW Moody Ave, KR-BSR Phone: 503-494-7062 Fax: 503-346-6931 Email: limje@ohsu.edu

SUMMARY OF CHANGES

#	Section	Change	Justification
2.0	1	Revised language	Background language has been revised to include additional information regarding immunotherapies, olaparib and durvalumab
2.0	1.5.1	Added additional risk language	Risk language regarding immune checkpoint blockade has been added per manufacturer recommendation
2.0	2.2, 2.3	Revised language	Objectives revised for clarity to align with study endpoints
2.0	3.1.1	Added scientific rationale for study design	Language in study design has been revised for clarity
2.0	3.1.1, 3.2.2, 6.3.3, 7.13	Changed to CTCAE v5.0	CTCAE 4.03 has been updated to CTCAE 5.0
2.0	3.2	Endpoints table revised for clarity	Endpoints times, start and stop, have been revised for clarity. Objectives have been added to align with endpoints.
2.0	4.1, 4.2	Inclusion criteria revised	Inclusion criteria revised for clarity
2.0	4.1	Inclusion life expectancy changed from >6 months to ≥16 weeks	Given the inclusion criteria allow up to 2 lines of therapy in the metastatic setting, and average survival for metastatic TNBC is around 15 months, 16 weeks expected life expectancy is more appropriate for this study.
2.0	4.2	Added exclusion criterion of: Participants with germline BRCA mutated TNBC will be excluded	Olaparib is FDA approved for treatment of metastatic BRCA mutated breast cancer. Additionally, this combination is being actively investigated in a separate trial for patients with metastatic BRCA mutated breast cancer.
2.0	4.2	Added exclusion criterion of: Participants with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.	Olaparib is associated with increased risk of MDS/AML, participants with MDS/AML are being excluded to minimize risk of disease exacerbation
2.0	4.2	Revised poor medical health exclusion criteria	Exclusion criteria for participants with poor medical health revised for clarity
2.0	4.2	Addition of exclusion criteria deferring to investigator	Exclusion criteria deferring to investigator added for clarity and safety
2.0	4.2.1	Revised exclusion criteria	Exclusion criteria is revised for clarity and minimize participant risk
2.0	5.1.1, 5.2.1	Revised drug acquisition for olaparib and durvalumab	Revised language for acquisition of olaparib and durvalumab
2.0	5.1.8	Revised administration language	Language for revised clarity
2.0	5.2.2	Updated language	Formulation packaging language revised per manufacturer recommendation
2.0	5.2.5, 5.2.6, 5.2.7.1	Updated language	Language revised per manufacturer recommendation

#	Section	Change	Justification
2.0	6.3.1, 6.3.1.1, 6.3.16, 6.3.2, 6.3.3 - 6.6.2	Updated language to toxicity management and supportive care	Language revised per manufacturer recommendation
2.0	7.4.3	Addition of fecal sample collection	Study added to characterize microbiome as part of understanding tumor resistance based on recent literature findings: Gopalakrishnan V,et al. Science. 2017;359(6371):97-103.
2.0	8.5.5	Added section “Confirmation of Progression Guidelines”	Confirmation of progression guidelines have been added i) for participant management and treatment decisions, and ii) in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of PD to distinguish pseudoprogression from true radiologic progression
2.0	9.2.1	Adverse Events	Language updated for clarity
2.0	9.2.2	Serious Adverse Events	Language updated for clarity
2.0	9.4.2	Olaparib Adverse of Events of Special Interest	Language added per manufacturer recommendation
2.0	9.4.3	Durvalumab Adverse of Events of Special Interest	Language added per manufacturer recommendation
2.0	9.5	Additional criteria added to AE assessment	Language added per manufacturer recommendation
2.0	9.5.1	Adverse events after the 90 day follow up period	Language added per manufacturer recommendation
2.0	9.6, 9.6.1, 9.6.2	Added Overdose language for olaparib and durvalumab	Additional safety reporting language added
2.0	9.7	Revised MedWatch reporting language	Revised language to include instruction for manufacturer reporting
2.0	9.8	Added Section “Reporting of deaths to AstraZeneca”	Added language to include instruction for manufacturer reporting
2.0	10.1, 10.2.2, 10.2.3.2, 10.3.2.1	Revised language	Statistical language revised for clarity
2.0	10.2.4	Addition of Analysis of Exploratory Endpoints	Statistical language added for exploratory endpoints
2.0	11.1	Revised language	Language revised for clarity
2.0	12.3	Added REDCap Cloud EDC	Revised to include description of REDCap Cloud EDC
2.0	12.5.1	Added specimen/data sharing language	Additional specimen/data sharing with existing observational study, MMTERT, IRB#16113
2.0	13.1, 13.5	Revised language	Revised for clarity
2.0	Appendix A	Revised language	Revised for clarity
2.0	Appendix C	Revised language	Revised language per manufacturer recommendations
2.0	Appendix H	Addition of Hy’s Law	Language added for identification/ actions required in cases of increases in

#	Section	Change	Justification
			liver biochemistry and evaluation of Hy's law cases
3.0	Overview	Updated the address for the Statistician	Contact information for Biostatistics Shared Resources updated
3.0	7.13 Schedule of Events	Collection of Tumor Markers updated	Collection of tumor markers on C1D15 and C2D15 has been added to monitor response to therapy by liquid blood biomarkers. Tumor markers are needed at the end of treatment to correlate liquid blood-based biomarkers to imaging to evaluate response to therapy.
3.0	7.13 Schedule of Events	Fecal Sample collection moved from follow-up to end of treatment in the schedule of events	The schedule of events was updated to align with Section 7.4.3. Fecal samples are to be collected at screening, before starting durvalumab, and at the time of disease progression.
4.0	4.2	Exclusion criteria #5 revised to state "Participant received prior chemotherapy within the past 28 days, prior targeted therapies within the past 14 days, or radiation (except for palliative reasons) within the past 3 weeks, prior to first day of treatment"	Exclusion criteria incorrectly stated limitation on prior therapy within past 3 weeks prior to going on study. A washout period of 14 days is sufficient to allow recovery from the side effects of targeted therapies.
4.0	7.4.2	Blood collection to occur at OHSU and CHO	Amended to correctly state that blood collection occurs at both OHSU and CHO study sites.
4.0	8	Revised definition to use irRECIST response criteria	Definition of immune response was amended from irRC to irRECIST to facilitate unidimensional measure of tumor response
5.0	Synopsis	Study Center: multicenter [U.S. Only]	Synopsis updated to reflect the study is multi-center
5.0	4.4.1.2	Multicenter Registration	Instructions for multicenter study registrations added
5.0	5.1.1.1, 5.2.1.1	Multicenter Acquisition	Instructions for multicenter study drug acquisition added
6.0	Synopsis, schema, 3.1, 6.1, 6.1.1, 6.4, 7.1.3	Initial treatment with olaparib monotherapy shortened from 4 weeks to 2 weeks	The treatment timeframe with olaparib monotherapy is reduced to better assess biological activity of study drug. The shortened timeframe also decreases the time to which participants can receive the combination of olaparib and durvalumab.
6.0	3.1, 7.4.1, 7.4.1.2, 7.1.3	Biopsy pre- and post- olaparib monotherapy reduced from 4 weeks to 2 weeks	Change in schedule is made to align with revised treatment period for olaparib monotherapy
6.0	4.1	Inclusion criteria revised to clarify prior anti- PD-1 or PD-L1 therapy is not allowed in the metastatic setting. Additional allowance for patients that received prior immunotherapy in the adjuvant	Changes to study eligibility made to reflect real-world experience with this patient population.

#	Section	Change	Justification
		setting.	
6.0	4.2	Reduced washout period from 28 days to 14 days	Changes to study eligibility made to reflect real-world experience with this patient population in that study agents can be safely initiated after this 14 day period.
6.0	4.3.1	Table 2 deleted	Projected accrual table removed as study is now multisite with subsites in OR, WA, and MN
6.0	7.2	Imaging revised to allow for CT, MRI, PET, or PET/CT	Changes to study eligibility made to reflect real-world experience with this patient population.
6.0	7.4	Revised tissue collection and processing	Revised for clarity
6.0	7.5	Updated GeneTrails Panel	Revised to reflect updated versioning of panel being utilized in OHSU site laboratory
7.0	Synopsis, 3.1, 6.1.1, 6.4	Lead-in treatment with olaparib monotherapy is increased from 14-days to 28-days	
7.0	Appendix C	Revised contraception requirement to 2 months	Revised to align with inclusion criteria requirement of 60 days.
7.0	7.4.3	Fecal sample collection is optional	Revised for clarity
7.0	7.1.7	Corrected “RT” to study therapy with regards to AE assessment	Correction of typographical error
7.0	7.7	Revised statement to denote what information is required for collection from individuals who are screen failures.	Revised for clarity
7.0	9.5	Corrected AE causality rating from “yes or no” to “definite, probable, unrelated.”	Correction of typographical error
7.0	9.5	Revised AE follow-up period to include last dose of study drug and not last day of study participation	Revised for clarity
7.0	9.5.1	Replaced durvalumab with study drug	Corrected typographical error to denote that there is more than one study drug
7.0	9.7.3	Revised consenting of participant’s whose sexual partner becomes pregnant	Corrected an incomplete statement.
7.0	10.1, 10.2.3.3	Revised requirements for conducting interim analysis to clarify that only 1 post-baseline disease assessment to conduct interim analysis	Revised for clarity
8.0	Synopsis, 3.1.1 3.2.1, 3.2.2	End timing of efficacy assessment (ORR, CBR, DOR) revised to End of treatment (previously 6 months post-treatment)	Revisions made to ensure clarity and consistency across protocol.

#	Section	Change	Justification
8.0	8.3.3	Objective response rate description corrected to include definition of assessment	Defintion corrected for accuracy to align with statistical analysis of ORR being assessed as the best overall response
9.0	The modifications in this version 9 of the protocol includes the addition of 3 new treatment arms. Following 28-day monotherapy with olaparib, a participant's tumor will be characterized using several clinically-validated assays, the results of which will be used to guide a treatment assignment comprising of olaparib in combination with durvalumab (Arm 1), capivasertib (Arm 2), or selumetinib (Arm 3), or ceralasertib monotherapy (Arm 4). The modifications included in this amendement detail the background and rationale for the addition of these investigational products to the study, along with justification to the changes in study design approach. Changes reflected in this amendment include the dosing guidelines and toxicity management for capivasertib, selumetinib, and ceralasertib, respectively, as well as requirements for drug-specific assessments, and known toxicities and adverse events for each drug agent. Changes to the study design and the statistical approach have also been added to Section 10. A description of the criteria guiding the decision logic for treatment arm assignment is provided in Section 3, and Appendix A. The total sample size for the revised study is increased up to n = 132.		
9.1	Cover page, Header	PI Change	PI Change
9.2	Cover page, Header	PI Change	PI Change

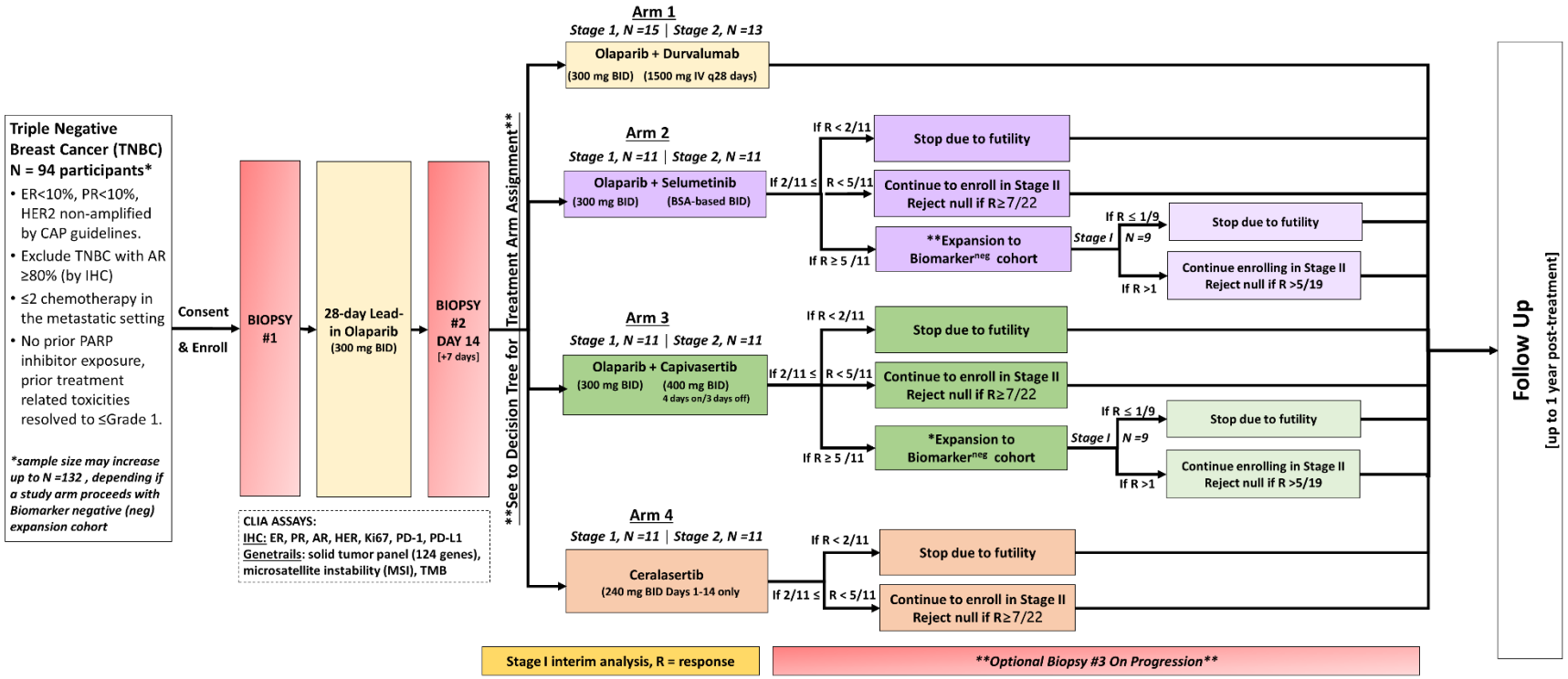
SYNOPSIS

Study Title	A Phase II, Open-Label, Study of Olaparib in combination with either Durvalumab (MEDI4736), Selumetinib, or Capivasertib, or Ceralasertib monotherapy in Patients with Metastatic Triple-Negative Breast Cancer
Protocol #	18504
Study Center	multicenter [U.S. only]
Clinical Phase	Phase II - Combination
Investigational Components	Olaparib - FDA Approved Drug - used for an unapproved purpose Durvalumab - FDA Approved Drug - used for an unapproved purpose Capivasertib - Investigational Drug Selumetinib - FDA Approved Drug - used for an unapproved purpose Ceralasertib - Investigational Drug
Interventional Study Type	*Multi-arm*
Précis	This is an open-label, non-comparative, multi-arm, Phase II study to assess the efficacy of combining olaparib with durvalumab (MEDI4736), capivasertib, or selumetinib, or ceralasertib monotherapy in the treatment of patients with metastatic triple-negative breast cancer (TNBC). All eligible participants with biopsy-proven TNBC will undergo a pre-treatment biopsy, after which they will receive a 28 (± 7) -day, single cycle, induction treatment of olaparib (300 mg, PO BID). At the 2 week mark, participants will then undergo a repeat on-treatment biopsy. After Cycle 1, participants will be assigned to receive olaparib as part of 4 potential treatment arms: olaparib and durvalumab (Arm 1), olaparib and selumetinib (Arm 2), olaparib and capivasertib (Arm 3), and ceralasertib monotherapy (Arm 4). Assignment to a study arm uses a decision-tree logic that is based on predefined molecular characteristics of the participant's tumor at baseline or following olaparib monotherapy. Combination therapy in each treatment arm will continue for 12 cycles until disease progression, unacceptable toxicity, or participant withdrawal, whichever occurs first. Participants will also be offered optional repeat biopsy on progression. This is a non-comparative study, and the efficacy and safety of the assigned study interventions for each treatment arm (i.e., Arm 1, Arm 2, Arm 3, or Arm 4) will be evaluated independently of one another. The primary endpoint of this study is to determine the overall response rate (ORR) for olaparib in combination with durvalumab, capivasertib, or selumetinib, or ceralasertib monotherapy. Secondary endpoints of efficacy measures include: clinical benefit rate (CBR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS),). Safety and tolerability of each proposed treatment arm will also be evaluated. Participant research tissue samples will be subject to comprehensive multi-omics, and an exploratory-based approach to evaluate predictive biomarkers of resistance to therapy and disease progression.
Primary Objectives	Assess the overall response to treatment

Secondary Objectives	1. Assess participant benefit from treatment 2. Determine the time to disease progression following response to study therapy 3. Determine time to first disease progression or death of participants enrolled on the study 4. Determine survival of participants enrolled on the study 5. Assess safety and tolerability of the proposed therapy
Exploratory Objectives	1. To assess a change in quality of life (QOL) measured by QLQC30 in each treatment arm. 2. To assess a change in QOL measured by QLQBR23 in each treatment arm. 3. Examine response rates depending on tumor characteristics 4. Identify predictive biomarkers of sensitivity to therapy 5. Identify emerging mechanism of resistance to therapy 6. Determine changes in tumor cells induced by PARP inhibitors 7. Identify predictive biomarkers to select combinatorial therapy that could overcome resistance to therapy
Primary Endpoints	1. ORR for olaparib combined with durvalumab (Arm 1) 2. ORR for olaparib combined with selumetinib (Arm 2) 3. ORR for olaparib combined with capivasertib (Arm 3) 4. ORR for ceralasertib (Arm 4)
Secondary Endpoints	1. CBR for each treatment Arm. 2. DOR for each treatment Arm. 3. PFS for each treatment Arm. 4. OS for each treatment Arm. 5. Incidence of ≥Grade 3 toxicities (per CTCAE 5.0) for each treatment arm
Exploratory Endpoints	1. Change From Baseline to end of treatment in EORTC QLQ-C30 2. Change From Baseline to end of treatment in EORTC QLQBR23
Number of Participants	Up to N=132
Duration of Therapy	Participants are planned to receive 13 cycles of therapy (approximately 52 weeks). Participants deriving clinical benefit from assigned treatment may, at the investigator's discretion and in the absence of disease progression or unacceptable toxicity, continue on therapy beyond the planned 13 cycles
Duration of Follow Up	12 months
Key Inclusion Criteria	• Participants with biopsy-proven metastatic TNBC defined as ER<10%, PR<10%, HER2 non-amplified by CAP guidelines. ○ Individuals with tumors showing androgen receptor (AR) ≥80% by immunohistochemistry are excluded from study participation. • Participants must have at least one measurable site of disease as defined by RECIST v1.1 that is amenable to biopsy. • Participants with or without germline *BRCA* mutated TNBC are eligible for study treatment. • Participants who have not received any prior systemic therapy for metastatic disease are eligible • ≤2 chemotherapy allowed in the metastatic setting, • ECOG PS ≤1,

	• No prior PARP inhibitor exposure in the metastatic setting, and prior treatment related toxicities resolved to ≤Grade 1.
Key Exclusion Criteria	• Known active autoimmune disease requiring steroid therapy or disease-modifying agents (Arm 1 only) • Uncontrolled Human Immunodeficiency Virus (HIV). Controlled HIV, defined as basal CD4+ T-cell count ≥200 cells/mm^3 and low-level viremia (< 60 copies/ml) is permitted. • Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). • Symptomatic brain metastases • Arm-specific exclusion criteria as described in protocol.
Statistical Considerations	**Arm 1:** A two-stage analysis will be performed using a Simon 2-stage Minimax design. The null (Immune checkpoint blockade alone) and alternative (Durvalumab and Olaparib) hypotheses are: H0: π = .15 and Ha: π =.35. For the primary endpoint, a total sample size of 28 participants will achieve 80 percent power to detect the overall response rate difference of 0.20 using the two-stage Minimax design with one-sided type I error = 0.05. The trial will be terminated in stage I if 2 or less out of the first 15 participants respond. If the trial goes on to the stage 2, a total of 28 participants will be studied. If the total number responding is less than or equal to 7, the drug is rejected. **Arms 2-4:** Fleming's two-stage design will be used. The null (PARPi monotherapy) and alternative (olaparib and capivasertib, selumetinib, or capivasertib) hypotheses are: H_0: π = 0.15 and H_a: π = 0.40. For the primary endpoint, a total sample size of 22 participants will achieve 80 percent power to detect the overall response rate difference of 0.25 with one-sided type I error=0.05. In the first stage, 11 patients will be accrued. If there are 1 or fewer responses in these 11 participants, the study will be terminated in stage 1. Otherwise, 11 additional participants will be accrued for a total of 22. The null hypothesis will be rejected if 7 or more responses are observed in 22 participants. If there are 5 or more responses in 11 participants, the arm will open for an expansion study with biomarker negative patients. ***Expansion for biomarker negative (Arms 2 & 3 only):*** A two-stage analysis will be performed using a Simon 2-stage Minimax design. The null (PARPi monotherapy) and alternative hypotheses are: H_0: π = 0.15 and H_a: π = 0.4. For the primary endpoint, a total sample size of 19 participants will achieve 80 percent power to detect the overall response rate difference of 0.25 using the two-stage Minimax design with one-sided type I error =0.05. The trial arm will be terminated in stage I if 1 or less out of the first 9 participants respond. If the trial arm goes on to stage 2, a total of 19 participants will be studied. The null hypothesis will be rejected if more than 5 responses are observed in 19 participants.
Efficacy Assessments	Overall response rate, Clinical Benefit Rate, Duration of Response, Progression-free survival, Overall survival
Safety Assessments	Adverse events will be collected and graded according to CTCAE 5.0

SCHEMATIC OF STUDY DESIGN



This is multi-arm, open-label, Phase II study to assess the efficacy of combining olaparib with durvalumab, selumetinib, or capivasertib, or ceralasertib monotherapy to treat patients with metastatic triple negative breast cancer (TNBC). This study will enroll participants with metastatic TNBC, defined as ER < 10%, PR < 10%, HER-2 non-amplified, and AR <80%. Eligible participants that consent to study will undergo a pre-treatment biopsy, following which patients will proceed to receive a single cycle (i.e., 28 days ±7days) of olaparib (300 mg, PO, BID). After 14 days of receiving olaparib monotherapy, participants will undergo a second on-treatment biopsy (Cycle 1, Day 14 [±7 days]). After completing the single cycle of olaparib monotherapy, participants will be assigned to one of four treatment arms based on predefined molecular tumor characteristics indentified pre- or post-treatment with olaparib monotherapy. Each treatment arm consists of participants receiving olaparib (300 mg BID) in combination with durvalumab (1500 mg, IV, q4week), selumetinib (BSA dosing per Table 15), or capivasertib (400 mg BID, 4 days on/3 days off), or ceralasertib monotherapy (240 mg BD days 1-14 of each cycle). Participants are planned to receive their assigned combination treatment for a total of 12 cycles. At the completion of all on-study procedures, participants will be considered off-treatment and be followed-up for disease and survival outcomes. Participants will be asked to submit an optional tumor biopsy in the event of disease progression. This a non-comparitive study, and each treatment arm will be independently evaluated. The primary endpoint is objective response rate following completion of assigned study therapy. Additional efficacy endpoints will be evaluated by assessing clinical benefit rate, duration of response, and survival. Safety of the on-study olaparib combination treatment arms and ceralasertib monotherapy will also be assessed. Exploratory research using patient biopsies that are sequentially collected will investigate the cellular and molecular biology of tumor cells to better understand emerging mechanisms of resistance to therapy.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACC	Advanced Computing Center
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
BID	Twice daily
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
CR	Complete response
CRC	Clinical Research Coordinator
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DLT	Dose limiting toxicity
DSDB	Double stranded DNA breaks
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HER2	Epidermal growth factor receptor, type 2
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Homologous recombination
HRBC	Hormone receptor positive breast cancer
HRD	Homologous recombination deficiency
IB	Investigator’s brochure
ICB	Immune checkpoint blockade
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IND	Investigational new drug application

IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
ORR	Overall response rate
PARP	polyADP ribose polymerase
PD	Progressive Disease
PET	Positron emission tomography
PI	Principle Investigator
PO	*Per os* (by mouth, orally)
PR	Progesterone receptor
Pr	Partial response
RBC	Red blood cell (count)
RNI	Reportable new information
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SSDB	Single stranded DNA breaks
TIL	Tumor Infiltrating Lymphocyte
TNBC	Triple negative breast cancer
TSMP	Trial Specific Monitoring Plan
ULN	Upper limit of normal
UP	Unanticipated problem
US	United States
WBC	White blood cell (count)

This document is intended to be gender neutral. The terms male and female, where stated, are used for identifying sex as a biological variable that is integral to medicine.

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BREAST CANCER EPIDEMIOLOGY

Breast cancer is the most common cancer type among women in the United States (US), with an estimated 252,710 new cases expected to occur in 2017 (SEER 2017) [1]. Breast cancer can be classified into three distinct subgroups based on the expression of the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor-2 (HER2). Hormone receptor-positive breast cancer (HRBC), defined as ER and/or PR positive (≥1%), is the most common subtype and constitutes around 70% of breast cancers. HER2-positive disease, characterized by HER2 gene amplification, represents around 15-20% of cases; and triple-negative breast cancer (TNBC) – defined as lacking ER and PR expression (<1%), and negative for HER2 gene amplification – represents around 15% of cases [2,3].

Despite advances in detection and treatment, breast cancer remains the second leading cause of death for women in the United States. Approximately 40,000 women are expected to die from the disease in 2017, with most deaths attributed to the development of incurable metastatic disease [4,5]. The clinical development of novel targeted therapies has extended survival for patients with metastatic breast cancer. In the metastatic setting, HRBC and HER2-positive disease have significantly better outcomes than TNBC [6]. However, virtually all patients develop resistance to treatment and eventually succumb to this disease. This stresses the urgent need for the development of novel treatment strategies to overcome resistance and improve outcomes in this poor prognosis population.

1.2 TNBC

TNBC accounts for 15-20% of all breast cancers and is more common in young women and women of African-American or Hispanic origin [7,8]. TNBC tumors tend to exhibit more aggressive features, have a higher tendency for metastasis, and overall worse prognosis compared to HRBC and HER2-amplified disease [8]. In clinical practice, TNBC is defined as a single entity lacking expression of ER and PR, and lack of HER2 gene amplification. However, molecular analyses of TNBC have proven this is a heterogeneous disease, with multiple identified subtypes characterized by specific gene expression profiles [9,10]. Patients with metastatic TNBC have a poor median survival of ~1 year following treatment with sequential single-agent chemotherapy [3,11,12]. Despite an improved understanding of TNBC biology, there are currently no targeted agents approved to salvage TNBC that is resistant to chemotherapy [13]. There is a need for innovative trial designs for evaluating novel therapies, identify resistance mechanisms, and inform the next generation of rational combinations to overcome resistance and improve outcomes in this poor prognosis disease.

1.2.1 PARP INHIBITORS IN *BRCA* ASSOCIATED BREAST CANCER

One of the most commonly dysregulated pathways in TNBC involves DNA damage response genes [9,10], including but not limited to *BRCA 1* and *BRCA2 (BRCA 1/2)* genes. Approximately 75% of breast cancers that arise in *BRCA1/2* carriers are TNBC [14]. BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo[15,16] and in the clinic.[17] This has prompted the use of DNA damaging therapies, such as platinum therapies [18] and poly ADP ribose polymerase (PARP) inhibitors in the treatment of TNBC. Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for

combination with chemotherapy and other anti-cancer agents. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies, and has been approved as monotherapy in advanced *BRCA1/2* mutant breast cancer. PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single-strand breaks (SSBs). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair.[19,20] Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double-strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Further PARPs play a key role in replication fork protection and their inhibition leads to replication fork collapse with acquisition of DNA damage.[21] Tumors with HR deficiencies (HRD), such as breast and ovarian cancers in patients with *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates[22]. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

In early-phase clinical trials, PARP inhibitors have shown clinical activity in patients with *BRCA* associated cancers, including breast cancer (**Table 1**). These findings led to the further development of PARP inhibitors for the treatment of *BRCA* associated breast cancer. The OLYMPIAD trial evaluated single-agent olaparib in patients with *BRCA* associated metastatic breast cancer who have received prior chemotherapy in the metastatic setting. In 302 evaluable patients, olaparib significantly improved overall response rate (ORR) (59.9 vs. 28.8%) and progression free survival (7.0 vs. 4.2 months, HR 0.58 (0.43 – 0.80), p<0.001) compared to physician choice chemotherapy [23]. This pivotal study led to the FDA approval of olaparib for the treatment of metastatic *BRCA1/2* associated metastatic breast cancer in January 2018, the first PARP inhibitor approved for breast cancer treatment. Additionally, the EMBRACA study evaluated talazoparib in a similar patient population to OLYMPIAD. In 431 evaluable patients, talazoparib significantly improved ORR (62.6 vs 26.2%, OR 4.99 (2.9 – 8.8), p<0.001) and progression free survival (8.6 vs 5.6 months, HR 0.54 (0.41 – 0.71), p<0.001) compared to physician choice chemotherapy [24].

Table 1. Single Agent PARP inhibitors in germline *BRCA* 1/2 associated cancers.

Drug	Patients	BCa (n)	Efficacy	
			Entire Study	**BCa**
Olaparib Phase 1[17]	60 patients BRCA1 28% BRCA2 8%	9	CBR 63% (BRCA mutated)	ORR 11%
Olaparib 400 mg BID[25]	27 patients BRCA1 67% BRCA2 33%	27	ORR 41%	-
Olaparib 400 mg BID[26]	298 patients BRCA1 60% BRCA2 40%	62	ORR 26.2%	ORR 13%

Table 1. Single Agent PARP inhibitors in germline *BRCA* 1/2 associated cancers.				
Drug	**Patients**	**BCa (n)**	**Efficacy**	
			Entire Study	**BCa**
Talazoparib Phase 1[27]	71 patients BRCA1 26% BRCA2 25%	14	N/A	ORR 50% CBR 86%
Talazoparib Phase 2	84 patients BRCA 100%	49 (prior platinum)	ORR 21%	-
		35 (no prior platinum)	ORR 37%	-
Niraparib Phase 1[28]	100 patients BRCA 29%	4	ORR 40% (BRCA mutated)	ORR 50%
CBR = clinical benefit rate; ORR = overall response rate				

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

1.3 IMMUNOTHERAPIES

It is increasingly understood that the immune system recognizes cancers, and, under some circumstances, the immune system may control or even eliminate tumors[29].

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T-cells[30]. It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273)[31]. The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T-cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit the immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages [32]. Importantly, PD-L1 is commonly overexpressed on tumor cells or non-transformed cells in the tumor microenvironment [33]. PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T-cells. These deactivated T-cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of anti-tumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance the anti-tumor immune response in cancer patients [34-39] with responses that tend to be more pronounced in patients with tumors that express PD-L1 [40-42]. In addition, high mutational burden (e.g., in bladder carcinoma [43]) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells [44]. Blockade of CTLA-4 binding to CD80/86 by anti–CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including the killing of established murine solid tumors and induction of protective anti-tumor immunity. Therefore, it is expected that treatment with an anti–CTLA-4 antibody will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

Preclinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, while nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1, agent have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

1.3.1 IMMUNE CHECKPOINT BLOCKADE IN TNBC

The recent advent of immune checkpoint blockade (ICB) has greatly advanced cancer therapy by improving efficacy and survival for a number of tumor types, especially those with high mutational burden and neo-antigens able to elicit anti-tumor immunity [33,36,45-52]. In patients with TNBC, which carries a higher mutational burden as compared to HRBC and HER2-amplified BC [53], treatment with single-agent ICB, Pembrolizumab (PD1 inhibitor), achieved a near 20% ORR, with some responses being durable [54]. Additionally, recent data suggest that ICB checkpoint blockade may achieve higher efficacy if used in earlier lines of therapy. In metastatic TNBC, ORR to frontline pembrolizumab are reported at 23%, compared to approximately 5% if patients who had received prior chemotherapy[55,56].

Similarly, treatment with Atezolizumab (PD-L1 inhibitor) achieved an ORR of 13% overall in patients with metastatic TNBC. In that study, the ORR was 26% with Atezolizumab frontline therapy, compared to 11% if used as second therapy or beyond [57]. Finally, the combination of Atezolizumab (PD-L1 inhibitor) with nab-Paclitaxel in metastatic TNBC was well tolerated, and resulted in a confirmed ORR of 42% in 32 evaluable patients, with highest response rates seen

in frontline therapy [58]. This combination is being evaluated in phase III as frontline therapy for metastatic TNBC (NCT02425891). Interestingly, patients whose tumors lacked PD-L1 expression also derived benefit from ICB [40,59-61]. These findings support the need for the continued development of robust biomarkers of sensitivity to ICB.

Efforts to understand breast tumor complexity have revealed an important relationship between the tumor and the immune system. In TNBC, tumor infiltration with cytotoxic T-lymphocytes (CTLs) ensuing chemotherapy-induced immunogenic cell death [62-64] is prognostic for improved survival [65,66] and predictive for response to NACT [67]. Unfortunately, only 11% of TNBCs have clinically significant CTL infiltrate (>50% infiltration) at presentation [67]. Moreover, not all tumor-infiltrating lymphocytes (TILs) are equal, and not all patients with high TIL infiltration have a good prognosis. Notably, the presence of $CD8^+$ TILs in residual disease after NACT is a positive prognostic marker for survival in TNBC, whereas tumors populated predominantly with regulatory $CD4^+$ TILs have poorer outcome [68,69]. These findings support the continued development of novel strategies to induce/augment CTL responses in TNBC. Indeed, we have demonstrated in our previous pilot study (NCT03544125) that PARP inhibitors can increase immune invasion in breast cancer and can convert an immune desert to an immune inflamed environment with marked duration of patient responses to the combination of olaparib and durvalumab (unpublished).

1.3.2 DURVALUMAB BACKGROUND/NON-CLINICAL AND CLINICAL EXPERIENCE

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure. Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; and are now fully merged designated AstraZeneca). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T-cells resulting in the restored proliferation of IFN-γ [70]. *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism [70]. Based on these data, durvalumab is expected to stimulate the patient's anti-tumor immune response by binding to PD-L1 and shifting the balance toward an anti-tumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.9.1.1 and Section 9.4.2. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy, and pharmacokinetics.

1.3.3 RATIONALE FOR DURVALUMAB FIXED DOSING

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady-state PK

concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady-state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others [71-74]. Wang and colleagues[73] investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters [74].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

1.4 PHOSPHOINOSITIDE 3 (PI3)-KINASE AND AKT SIGNALING IN TNBC

Alterations in the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway are common genomic abnormalities across breast cancer subtypes.[75] This includes both mutational events and pathway activation independent of mutations. The PI3K/AKT/mTOR pathway is essential in promoting tumor cell growth and survival. In general, the pathway is activated when receptor tyrosine kinases elicit activation of PI3K, followed by phosphorylation and activation of AKT and eventual downstream targets such as mTOR.[75] In TNBC, several mechanisms for constitutive activation of the PI3K/AKT/mTOR pathway include overexpression of upstream regulators (e.g., receptor tyrosine kinase [RTKs] such as epidermal growth factor receptor [EGFR]), activating mutations to PI3K catalytic subunit α (PIK3CA), as well as loss of function or expression of phosphatase and tensin homolog (PTEN) and the proline-rich inositol polyphosphatase PLHP2.[75-77] Though rare, activating mutations to AKT and mTOR have also been reported.[78] Additionally, p53 inactivation has also been proposed to enhance the PI3K pathway.[75,79] Subsequent efforts to advance the clinical development of PI3K pathway inhibitors have been bolstered by the clinical success of the mTOR inhibitor, everolimus, which is FDA-approved for hormone receptor-positive, HER2-negative breast cancer.[80] These include the clinical development of other PI3K pathway inhibitors such as those targeting PI3K and AKT with PI3K inhibitors being recently approved by the FDA.[78,80-86]

1.4.1 COMBINED INHIBITION OF PI3K SIGNALING AND PARP

Among its many roles, the PI3K/AKT/mTOR pathway is important in stabilizing and preserving DNA double-strand break repairs by interacting with the homologous recombination complex and is necessary for DNA repair during ionizing radiation.[87] Interestingly, the inhibition of PI3K has been proposed to decrease BRCA1/2 expression and lead to homologous recombination deficiencies. Moreover, in BRCA-proficient and BRCA-1 mutated TNBC models, the dual inhibition of PI3K with BKM120 coupled with olaparib-mediated PARP inhibition, is effective in reducing tumor cell growth proliferation and had synergistic in vivo anti-tumor effects.[88,89] These and other findings have provided the basis for formal clinical trials to evaluate the combined PARP and PI3K pathway inhibition by our and other groups.[90-93]

Matulonis et al.[90] reported on the safety and efficacy of combining a non-selective PI3K inhibitor, BKM120, and olaparib in patients with breast and ovarian cancers. Though no complete response was observed, the authors reported response rates (i.e., PR only) of 29% and 28% among the ovarian and breast cancer patients, respectively, that had measurable disease.

Using an accelerated intrapatient dose-escalation schema, Michalarea et al[92] evaluated the safety of combining olaparib with the AKT inhibitor, capivasertib (AZD5363) in 20 patients with advanced cancers. The established RP2D reported was capivasertib (AZD5363) at a dose of 640 mg (PO) twice daily for 2 of 7 days, and olaparib (300 mg PO) given twice daily as part of a 21-day cycle. Common (>15%) grade 1-2 toxicities observed were nausea, vomiting, fatigue, diarrhea, and anemia. The authors descriptively reported that PR was achieved and maintained for 6 months in a platinum-resistant ovarian cancer patient that characterized as being BRCA wild-type with PTEN LOH. A similar PR achieved in another platinum-resistant ovarian cancer patient with a BRCA1 mutant lasted for greater than 5.5 months (at the time of reporting). An additional but unconfirmed, PR was also seen in a patient with BRCA1-mutant breast cancer that was maintained for (2.5 months at the time of reporting).

An ongoing phase I/II trial (NCT02208375) has sought to evaluate the safety and efficacy of olaparib in combination with the mTORC1/2 inhibitor, vistusertib (AZD2014), or the AKT inhibitor, capivasertib (AZD5363), for the treatment of patients with recurrent TNBC, endometrial, ovarian, primary peritoneal, or fallopian tube cancer.[91,93] In the phase I portion of the trial evaluating the olaparib in combination with vistusertib (AZD2014), researchers reported a response rate of 19% and clinical benefit rate (CBR) of 34% (among 64 patients evaluable for response). Across diseases, a response rate of 27%, 20%, and 6% were reported for endometrial, ovarian, and breast cancer, respectively.[91] For the combination of olaparib and capivasertib (AZD5363), an overall response rate of 24% was achieved (among 30 patients evaluable for response); including, 7 confirmed partial responses (1 ovarian, 4 endometrial and 2 TNBC). The response rate among patients with endometrial cancer was 50% (4/8). Moreover, 6 additional patients had stable disease for greater than 4 months. The RP2D established confirmed that olaparib (300 mg PO BID) and capivasertib (320 mg PO, BID) administered on a 4 day on/3 day off schedule was tolerable. Notably, the majority of patients (86%), combined from both phase I portions of the trial, were BRCA wild-type, further suggesting that PARP inhibition appears effective even in the absence of BRCA-associated and/or HR-deficiencies.[93] Altogether, these clinical findings provide preliminary evidence of synergism between olaparib and inhibition of PI3K/AKT/mTOR signaling, and warrants further investigation.

1.4.1.1 *AKT inhibitor - Capivasertib (AZD5363)*

Capivasertib (AZD5363) is a pan-AKT inhibitor currently under clinical development. Refer to the investigator's brochure for additional details.

In the PAKT trial, the safety and efficacy of capivasertib plus paclitaxel was assessed as first-line therapy in women with previously untreated, metastatic TNBC.[86] In this study, 140 women (median age, 54 years) were randomly assigned to receive 90 mg/m² paclitaxel on days 1, 8 and 15, along with 400 mg twice-daily capivasertib (n = 70) or placebo (n = 70) every 28 days. Participants were treated until disease progression or unacceptable toxicity. Median follow-up was 18.2 months (95% CI, 13.5-24). The authors reported a median PFS of 5.9 months in the capivasertib group vs. 4.2 months in the placebo group (HR = 0.74; 95% CI, 0.5-1.08). In the capivasertib group, the median OS was 19.1 months, whereas the median OS was 12.6 months

in the placebo group (HR = 0.61; 95% CI, 0.37-0.99). More women in the capivasertib group experienced grade 3 to grade 4 diarrhea (13.2% vs. 1%), infection (4.4% vs. 1%), fatigue (4.4% vs. 0%) and rash (4.4% vs. 0%).[86]

The FAKTION trial was a randomized, double-blind, placebo-controlled, phase 2 trial for postmenopausal women with ER-positive, HER2-negative, metastatic or locally advanced breast cancer that had relapsed or progressed on an aromatase inhibitor.[94] Participants were randomly assigned to receive fulvestrant plus capivasertib (n=69) or fulvestrant plus placebo (n=71). The median PFS was 10.3 months (95% CI 5.0–13.2) in the capivasertib group and 4.8 months (3.1–7.7) among those randomized to the placebo group. An ORR in the capivasertib group was 41%, compared to 12% in the placebo group. The most common grade 3–4 AEs observed included: hypertension (22 [32%] of 69 patients in the capivasertib group vs 17 [24%] of 71 in the placebo group), diarrhea (10 [14%] vs three [4%]), rash (14 [20%] vs 0), infection (4 [6%] vs 2 [3%]), and fatigue (1 [1%] vs 3 [4%]). SAEs were only observed in the capivasertib group, including - and were acute kidney injury (2), diarrhea (3), rash (2), hyperglycemia (1), loss of consciousness (1), sepsis (1), and vomiting (1). The authors reported 1 death due to atypical pulmonary infection that was assessed as possibly related to capivasertib treatment.

1.5 RAS-RAF-MEK-ERK SIGNALING IN TNBC

The Ras-Raf-MEK-ERK pathway is initiated by activation of RAS by growth factor receptors with subsequent activation of a Raf-Mek-Erk cascade. The cascade includes 2 isoforms of mitogen-activated protein/extracellular signal-regulated kinase (MEK1/2), and 2 isoforms of extracellular signal-regulated kinase (ERK1/2). Activation of MEK1/2 catalyzes the phosphorylation of ERK1/2, which in turn phosphorylates numerous cytoplasmic (e.g., p90Rsk and IKK) and nuclear (e.g., Ets-1, Elk-1, c-Fos, c-Jun and c-Myc) targets.[95] Dysregulation of the Raf-MEK-ERK pathway is commonly observed in numerous epithelial cancers and is important in driving cell cycle progression, proliferation, invasion, and survival.[95] Though < 2% of primary breast cancer have mutations in the pathway constituents such as Ras and Raf, overexpression of receptor tyrosine kinases (e.g., EGFR) and copy number alterations in pathway constituents (e.g., amplifications or gains of KRAS and BRAF) can drive aberrant stimulation of the Raf-MEK-ERK pathway.[96-98] Moreover, crosstalk with the pro-survival PI3K/AKT, as well as loss of PTEN or regulatory microRNAs (e.g., Let-7) are also shown to promote altered Ras-Raf-MEK-ERK signalling.[99-101] Indeed approximately 30% TNBC have evidence of RAS pathway activation.

Preclinical evidence using TNBC cell lines suggests that targeted inhibition of Ras-Raf-MEK-ERK signaling reduces the proliferation and migration, and causes apoptosis and G1 arrest.[102-104] However, the potential for acquired resistance with individually targeting the Raf-MEK-ERK pathway suggests that inhibiting its signaling likely needs to be combined with targeted agents that block other pathways in order to reverse drug resistance.[105-108] As such, the clinical utility of targeting Raf-MEK-ERK signaling as part of a therapeutic combination in patients with breast cancer is currently underway (NCT01467310, NCT01138085, NCT01964924, NCT02685657, NCT025583542).[109-111]

Brufsky et al[111] reported on preliminary findings from Cohort I of the COLET trial (NCT02322814), in which patients with TNBC were randomized to receive paclitaxel alone or the combination of paclitaxel and the MEK inhibitor, cobimetinib. The combination of paclitaxel and cobimetinib achieved an ORR of 18%, whereas those that received paclitaxel alone attained an ORR of 9% (all partial responses). The median PFS was also increased with the

addition of cobimetinib (5.5 months vs. 3.8 months). In cohorts II and III of the COLET trial, the effects cobimetinib and atezolizumab were examined either paclitaxel or nab-paclitaxel, respectively. The majority of participants (~65%) in either cohort II or III had received prior treatment with a taxane. The researchers observed that the combination of cobimetinib, atezolizumab, and paclitaxel, achieved similar responses to those that received cobimetinib, atezolizumab, and nab-paclitaxel (34% vs. 29%). Interestingly, for patients that were PD-L1–positive, there was a higher response attained among these individuals in receiving paclitaxel compared to nab-paclitaxel (ORR 44% vs. 33%).[112]

1.5.1 COMBINED INHIBITION OF PARP AND RAF-MEK-ERK SIGNALING

Preclinical evidence shows that cell lines rendered resistant to PARPi are characterized by increased activation/expression of proteins within the RAS/MAPK pathway, suggesting that this pathway has a role in mediating PARPi resistance.[113] In tumor cells derived from breast, ovarian, and pancreatic cancers, which harbor RAS mutations, combined treatment with a PARPi and MEK inhibitor (MEKi) functions synergistically to elicit cytotoxic effects both in vitro and in vivo. Moreover, the effects of the PARPi and MEKi combinations were observed as being independent of BRCA1/2 and p53 mutation status. This suggests that combined inhibition of PARP and MEK may allow for a more generalizable approach to being able to treat patients with tumors lacking mutations in genes comprising HR machinery.[113] In line with these findings, the combination of a PARPi and MEKi is currently being explored in the clinic for the treatment of a variety of solid tumors (NCT03162627, NCT03695380, NCT03182673).[114]

1.5.1.1 *MEK inhibitor - Selumetinib (AZD6244)*

Selumetinib (AZD6244) is an orally available, selective inhibitor of MEK1 and MEK2 that is approved for pediatric patients, 2 years of age and older, with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).currently under clinical development. Refer to the investigator's brochure for additional details.

Efficacy of selumetinib was investigated in SPRINT (NCT01362803), a National Cancer Institute (NCI) sponsored, open-label, multicenter, single-arm trial in pediatric patients with NF1 and a measurable target PN that could not be surgically removed without risk of substantial morbidity. Patients in the efficacy population (n=50) were also required to have at least one significant morbidity related to the target PN. Morbidities present in ≥20% of patients included disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment, and bladder/bowel dysfunction. Patients received selumetinib 25 mg/m^2 orally twice a day until disease progression or unacceptable toxicity. The reported ORR was 66% (n=33; 95% CI: 51,79), all of whom achieved a partial response, with the majority (82%) of these responders sustaining their responses for ≥ 12 months. [115]

The anti-tumor activity of selumetinib is also currently being investigated in a variety of adult cancer types as a monotherapy or in combination with chemotherapies or other targeted agents.[116-130] While early phase trials of selumetinib monotherapy in adults with advanced solid tumors was suggestive of target inhibition and tumor response, only modest clinical activity was observed in a phase 2 of patients with NSCLC.[116,117,131] Several studies assessing selumetinib in combination with chemotherapies or other targeted agents (e.g., docetaxel, decarbazine, erlotinib) have reported manageable safety and tolerability profiles, often establishing a MTD or RP2D for selumetinib of 75 mg BID when administered as part of a combination regimen.[119,129,132,133]

Building on a similar approach, Kurnit et al[114] provided findings of a phase 1 dose-finding study examining the combination of olaparib and selumetinib among 14 patients with advanced solid tumors. No dose-limiting toxicities were observed for any of three dose levels were evaluated, and olaparib (300 mg PO, BID) and selumetinib (75 mg PO, BID) was established as the RP2D. No grade 4 AEs were observed. Reported grade 3 AEs occurred with equal frequency (7%): fatigue, elevated aspartate aminotransferase, decreased white blood cell count, elevated CPK, acneiform rash, and other skin effects. The most common AE (any grade) reported was anemia and hypophosphatemia (79% each). Twelve of the 14 patients were evaluable for response assessment. The combination resulted in an ORR of 17%, and a CBR of 33% (defined as CR, PR, and SD for ≥ 4 months). A PR was achieved in 2 patients (1 patient with KRAS mutant primary peritoneal cancer, and 1 with NRAS mutant ovarian cancer). At the time of reporting, 2 patients remained on treatment for >15 months (1 patient with KRAS mutant primary peritoneal cancer, and 1 patient with KRAS mutant non-small cell lung cancer). Notably, all patients achieving clinical benefit had BRCA wildtype-cancers.

1.6 ATAXIA TELANGIECTASIA AND RAD3-RELATED PROTEIN (ATR) SIGNALING IN TNBC

Response to single-strand (ss) DNA damage is mediated by ataxia telangiectasia and Rad3-related (ATR) checkpoint kinase 1 (CHK1) signaling.[134] When ssDNA occurs at sites of DNA damage or stressed replication forks, replication protein A-coated ssDNA recruits ATR and its binding partner, ATR interacting protein (ATRIP). This event triggers ATR to phosphorylate CHK1, which in turn promotes the proteasomal degradation of CDC25A that leads to decreased CDK2 activity, thereby suppressing G2-M transition and slowing S phase.[134] ATR is an essential mediator of cellular response to DNA replication stress that is often elevated in many cancers, including TNBC.[135] Notably, loss of G1 cell cycle checkpoint control arising from nearly ubiquitous presence of TP53 mutations is a recurring defect that causes even greater reliance on ATR-mediated intra-S and G2/M checkpoints following DNA damage.[136] Preclinical studies have shown that in cells lacking ATM, p53, or PTEN, the inhibition of ATR can promote synthetic lethality, and appears to enhance the cytotoxic effects of chemotherapies (e.g., gemcitabine, cisplatin, doxorubicin) and radiotherapy.[134,137-144] Given its importance in sustaining cancer cell viability, several ongoing clinical trials have sought to evaluate ATR inhibitors either alone or as part of a combination therapeutic regimen (**Table 2**).

Table 2. Summary of ATR inhibitors under clinical investigation.

ATRi	Target cancer type [Trial Identifier]	Treatment	Biomarker selection
M6620 (VX-970)	Advanced solid tumor [NCT03309150]	Alone or with carboplatin/paclitaxel	
	Advanced solid tumor [NCT02157792]	Gemcitabine, cisplatin, etoposide, or carboplatin	*TP53* mutation of *ATM* loss
	Advanced solid tumor [NCT02595931]	Irinotecan	
	Small-cell cancers [NCT02487095]	Topotecan	DDR pathway mutations
	Urothelial carcinoma [NCT02567409]	Cisplatin or gemcitabine	p53, p21, and *ERCC2* mutations

Table 2. Summary of ATR inhibitors under clinical investigation.

ATRi	Target cancer type [Trial Identifier]	Treatment	Biomarker selection
	Ovarian cancer [NCT02627443]	Carboplatin + gemcitabine	DNA damage assay, HRR mutations
	Ovarian cancer [NCT02595892]	Gemcitabine	
	mCRPC [NCT03517969]	Carboplatin ± docetaxel	
	Advanced solid tumor [NCT02723864]	Cisplatin + veliparib	DNA damage and apoptotic assay
	HNSCC [NCT02567422]	Cisplatin + XRT	DNA damage assay
	Brain metastases [NCT02589522]	Whole brain XRT	ATR, CHK1, RAD51, cyclin E, DNA-PK assay
M4344	Advanced solid tumor [NCT02278250]	Carboplatin, gemcitabine, or cisplatin	
Ceralasertib (AZD6738)	CLL, PLL or B-cell lymphoma [NCT01955668]	Alone	ATR targeted inhibition biomarker
	HNSCC [NCT03022409]	Alone	TH1/IFNγ gene and TIL state
	Refractory CLL [NCT03328273]	Acalabrutinib	
	Advanced solid tumor [NCT02630199]	Paclitaxel	
	Advanced solid tumor [NCT02264678]	Carboplatin, olaparib, or durvalumab	*ATM* deficiency
	TNBC [NCT03330847]	Olaparib	HRR mutations
	Advanced tumor [NCT02576444]	Olaparib	
	SCLC [NCT03428607]	Olaparib	
	Ovarian cancer [NCT03462342]	Olaparib	
	NSCLC [NCT03334617]	Durvalumab	
	Advanced solid tumor [NCT02223923]	XRT	
BAY1895344	Solid tumor and lymphoma [NCT03188965]	Alone	

Adapted from Mei et al.[137]

1.6.1.1 *ATR inhibitor - Ceralasertib (AZD6738)*

Ceralasertib (AZD6738), a potent, selective inhibitor of ATR that is under clinical investigation in several early-stage (phase 1 and 2) clinical trials for the treatment of solid and hematological malignancies. Please refer to the ceralasertib investigator brochure for additional details.

Ceralasertib monotherapy was explored in the PATRIOT collaborator study, where it was escalated on a continuous schedule in patients with advanced solid tumors.[145] The MTD was 160 mg BID. In an expansion of PATRIOT, which included provision to investgate different schedules, an intermittent schedule of 160 mg BD ceralasertib days 1-14 every 28 days was much better tolerated than continuous dosing. The PATRIOT study declared 160 mg BID ceralasertib on an intermittent schedule a futue RP2D (1915 - A Phase I study of ATR inhibitor, AZD6738, as monotherapy in advanced solid tumours (PATRIOT Part A, B).[146] The PATRIOT study did not permit escalation of the 160 mg BID dose on an intermittent schedule. However, 240 mg BD days 1-14 has been tested in combination with durvalumab in a company sponsored trial and with paclitaxel in a collaborator trial, and found to be tolerated. The confirmed RP2D for ceralasertib monotherapy is 240 mg BID for days 1-14 of every 28 day cycle.

Results from preclinical studies suggest that the cytotoxicity mediated by PARP inhibitors can be further potentiated by targeting the G2/M cell cycle checkpoint to force mitotic entry in the presence of DNA lesions.[142,147,148] The clinical efficacy of combined ATR and PARP inhibition has, unfortunately, not been fully realized. The phase 2 VIOLETTE study of patients with TNBC is assessing the efficacy of olaparib in combination with ceralasertib or the wee1 inhibitor, adavosertib (NCT03330847).[149] This combination of olaparib and ceralasertib, however, did not meet its predefined criteria for efficacy in the BRCA-mutant stratum and the study was closed early. These findings have instead prompted interest in evaluating ceralasertib as a monotherapy, but at a higher dose than that used in VIOLETTE. The study described herein will investigate the effects of single agent ceralasertib.

The dose of ceralasertib as monotherapy to be studied is 240 mg twice daily from Day 1 to Day 14 of every 28-day cycle. This dose has been used as monotherapy and in combination with durvalumab 1500 mg administered on Day 1 of each 28-day cycle in Study D5330C00004 (NCT02264678) where 29 patients with NSCLC and SCHNN have been treated. Ceralasertib 240 mg twice daily was given as monotherapy in Cycle 0 for 14 days (Days 1 to 14) and then from Day 15 to Day 28 in each subsequent cycle in combination with durvalumab.

Ceralasertib 240 mg twice daily from Day 15 to Day 28 of every 28-day cycle in combination with durvalumab 1500 mg administered on Day 1 of each 28-day cycle is also used in an ongoing collaborator (ESR) study in South Korea in patients with malignant melanoma (27 patients) and metastatic gastric cancer (31 patients) (as of 30 April 2020) (NCT02630199). This dose schedule of AZD6738 was not formally tested in PATRIOT (NCT02223923) in which 160 mg twice daily from Day 1 to Day 14 of every 28-day cycle, administered to 20 patients in the expansion cohort, was well-tolerated.

Preliminary safety data has shown that ceralasertib 240 mg twice daily from Day 1 to Day 14 of every 28 day cycle is well tolerated as monotherapy as well as in combination with durvalumab (Study D5330C00004).

The dose level of 240 mg twice daily is predicted to maintain ceralasertib concentrations above the estimated concentration of an inhibitor where ATR catalytic activity is reduced by 90%

(IC90) threshold for 12 hours in 90% of patients. A sigmoid model links ceralasertib monotherapy exposure with the difference between monocytes (PD modulation) and platelet decrease (the main related haematological toxicity of ceralasertib).

Based on the aforementioned data, the use of ceralasertib 240 mg twice daily as monotherapy from Day 1 to Day 14 of every 28-day cycle in this module is justified. Notably, ceralasertib 240 mg twice daily as monotherapy from Day 1 to Day 14 will also be administrated in the study PLANETTE (study title "A Modular Phase 2a, Open Label, Multicentre Study to Investigate DNA-Damage Response Agents [or Combinations] in Patients with Advanced Cancer whose Tumours contain Molecular Alterations") in which at least 25 patients with advanced solid tumours and 27 patients with mCRPC will initially be enrolled.

1.7 **RATIONALE**

Preclinical and clinical data have validated the efficacy of PARP inhibitors through synthetic lethality in tumors homologous recombination deficiency (HRD). However, it rapidly became clear that PARP inhibitors trapped PARP on DNA, creating double-strand breaks (DSB) that are difficult to repair [150]. Furthermore, PARP is a component of the replication fork, and inhibition of PARP results in replication fork collapse and induction of DNA damage.[21] The PARP trapping activity clearly contributes to both efficacy and toxicity, as the phase II doses for trapping PARP inhibitors correlate with their trapping activity and not with their ability to inhibit PARP enzyme activity. Thus, two approaches could increase the utility of PARP inhibitors: first, to induce HRD in HR competent cells and secondly, to capitalize on DNA damage induced by PARP and the toxic DSB induced by PARP trapping. Clinical trials have shown high response rates for PARP inhibitors in *BRCA* associated TNBC, with a more limited set of responses in *BRCA* wild-type TNBC showing a DNA damage repair signature.[27,151] Unfortunately, responses are not durable, stressing the need to understand resistance mechanisms to PARP inhibitors and develop combination therapies to improve responses.

Multiple mechanisms of resistance to PARP inhibitors have been identified, with most mechanisms based on preclinical models. Resistance falls into two broad categories; endogenous resistance due to increased HR repair capacity such as that mediated by RAS mutations [113] and acquired mechanisms of resistance, which fall into three categories: (a) reconstitution of HR competence indicated by reconstitution of Rad51 foci [150,152-155], (b) replication fork protection and (c) a miscellaneous group with multiple different mechanisms [150,156-158]. There is mounting evidence showing that PARP inhibition induces activation of numerous signaling pathways (i.e., PI3K-AKT, Raf-MEK-ERK), as well as immune activation.[159] Exploiting the crosstalk among these pathways, the Adaptive Multi-Drug Treatment of Evolving Cancers (AMTEC) study will investigate the combined inhibition of PARP with AKT, MEK, or PD-L1, as well as ATR inhibition alone, as a novel means to improve outcomes of patients with metastatic TNBC. In this study, participant assignment to a study arm will be informed using a decision-tree algorithm that utilizes biomarker-driven signatures indicative of immune cell activation, or perturbations in PI3K-AKT or Raf-MEK-ERK signaling, which can be exploited using targeted agents (refer to Section 3.1 and Appendix A).

1.7.1 TARGETING PARP AND THE IMMUNE RESPONSE

Additionally, preclinical studies have demonstrated immunomodulatory properties for PARP inhibitors through increased antigen presentation as well as recruitment of cytotoxic T-lymphocytes [160,161], both properties that may predict benefit of immune checkpoint blockade (ICB). Importantly, we have demonstrated PARP inhibitors and ICB are synergistic in syngeneic breast cancer models that are *BRCA1/2* wild type and competent for DNA damage repair through induction of a STING response (Fig.1). Importantly, multiple PARP inhibitor and ICB trials are underway, with preliminary and exciting emerging clinical trial data.

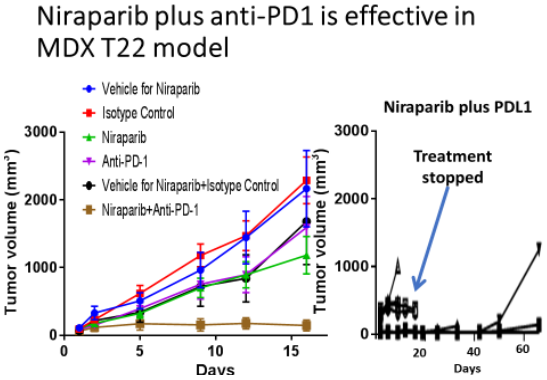


Figure 1. Efficacy of Niraparib and Anti-PD-1 in a xenograft mouse breast cancer model

In the TOPACIO trial, the combination of niraparib and pembrolizumab in patients with platinum-resistant ovarian cancer and TNBC was shown to be well-tolerated and had clinical activity in *BRCA*-mutant with a lower rate of response in *BRCA*-wildtype tumors [162]. Additionally, the MEDIOLA study reported the combination of olaparib and durvalumab (MEDI4736) in metastatic *BRCA* associated breast cancer to be well-tolerated, and have excellent disease control rate on preliminary analysis.[163] Finally, the proposed dosing combination of olaparib 300 mg orally twice daily and durvalumab at 1500 mg IV every 4 weeks has been reported to be safe and well-tolerated in a phase 1 study looking at recurrent women's cancers, including TNBC[164]. No dose-limiting toxicities were reported with the combination of olaparib and durvalumab, and the majority of adverse events were grade 1-2[164].

This study arm will focus on patients with *BRCA*-wildtype biopsy-proven metastatic TNBC. PARP inhibitors and ICB have each shown single-agent activity in TNBC. The preclinical and clinical data (Section 1.2) validate the rationale for combining PARP inhibitors with ICB for the treatment of metastatic TNBC, including patients without abnormalities in *BRCA1/2*, with the aims of augmenting responses to therapy and, more importantly, achieving durable responses in this poor prognosis population.

1.7.2 COMBINED TARGETING OF PARP AND CAPIVASERTIB

The preliminary evidence showing synergy in the combined inhibition of PARP and components of the PI3K-AKT pathway in several solid tumors, including TNBC, is compelling.[90-93] Moreover, the enhanced sensitivity to PARP inhibitors following inhibition of PI3K-AKT signaling occurs in both BRCA-proficient and -deficient TNBC cells, suggesting that a novel treatment strategy is possible regardless of BRCA mutational status.[88,165,166] Additional clinical information is critically-needed to fully understand the therapeutic potential of this combination in the treatment of TNBC and, in particular, biomarkers able to identify the subpopulation of patients likely to benefit from the combination. In the current study, patient-specific selection criteria will be used to guide the assignment of participants to receive the combination of olaparib and capivasertib. The dosing for this combination is based on a previous phase 1 trials that established olaparib (300 mg PO BID) and capivasertib (400 mg PO, BID) administered on a 4 day on/3 day off schedule as being safe and tolerable.[93]

1.7.3 COMBINED TARGETING OF PARP AND SELUMETINIB

The combined inhibition of PARP and MEK provides a compelling strategy to increase apoptosis in a variety of solid tumors. Particularly, the inhibition of MEK alters the apoptotic balance, induces deficiencies in homologous repair mechanisms, and reduces DNA damage checkpoint activity.[113] Translating these findings to the clinic, however, has yet to be fully explored, and it remains unknown if patients with TNBC can benefit from this combined treatment approach. In the current study, participants assigned to this treatment cohort will receive olaparib (300 mg PO, BID) and selumetinib (75 mg PO, BID) based on previously established RP2D.[114]

1.7.4 ATR TARGETING BY CERALASERTIB

The activated ATR-Chk1 pathway affects multiple DNA damage and replication checkpoint responses. Inhibiting ATR alters the G2/M cell cycle checkpoint to promote early mitotic entry even with DNA lesions present.[137,167] Given the prevalence of DNA damage repair defects in TNBC, targeting ATR for inhibition is a relevant strategy to increasing DNA damage and inducing mitotic crisis. To further explore the anti-tumor effects of ATR inhibition in TNBC, participants that do not have a molecular signature indicative of immune cell activation, or perturbations to AKT or MEK signaling, will be assigned to receive ceralasertib. In this treatment arm, participants will receive ceralasertib monotherapy (240 mg PO BID) on days 1 to 14 of each 28 day cycle.

1.8 **EXPLORATORY STUDIES BACKGROUND**

Rapid improvements in biomedical technology have revolutionized our understanding of cancer biology and allowed us to map the genetic landscape for different tumors. While novel therapies targeting cancer-specific alterations have generated responses, these are typically short-lived, and resistance to single-agent therapy almost universally emerges. There is a need to understand mechanisms of resistance to therapy and develop rational combinations able to augment and extend responses to treatment. Based on our institutional experience, serial metastatic breast cancer biopsies are safe and provide high yield samples for multi-omics analysis. To this end, the proposed study includes an adaptive biomarker platform that leverages serial tissue collection which can be correlated with clinical responses to therapies to inform on predictive biomarkers. This aims to:

a) Identify mechanisms of (1) adaptive (2) immunologic and (3) tumor microenvironmental sources of resistance to therapy
b) Develop strategies to induce synthetic lethality, rewire the tumor microenvironment, manage tumor heterogeneity and bypass adaptive resistance to therapy, and establish methods to optimize combinatorial therapy selection through real-time pharmacologic evaluation for participants
c) Achieve durable response rates with acceptable toxicity.

1.8.1 PRE-TREATMENT BIOPSY:

This biopsy will provide an unperturbed initial assessment of tumor biology, following which participants will proceed with monotherapy for 4 weeks of treatment. All pre-treatment biopsies will undergo clinically validated (i.e., CLIA) assays (Refer to Section 7.5).

1.8.2 ON-TREATMENT BIOPSY:

A repeat on-treatment biopsy will be performed after participants have completed a 2-week induction of olaparib monotherapy. Following single-agent therapy, the multi-omics performed on this repeat biopsy will allow for a deeper analysis of tumor biology through: confirming

pharmacodynamics effects of the monotherapy agent (i.e., confirmation of drug hitting target), revealing how the tumor ecosystem has adapted to therapeutic stress and identifying emerging mechanisms of resistance and therapeutic opportunities such as immune system activation.

1.8.3 POST-PROGRESSION BIOPSY:

This optional biopsy will inform on mechanisms of tumor escape from combination therapies. Findings from multi-omics analysis of this tissue sample can be compared to the on-treatment biopsy results to reveal mechanisms of resistance to mono vs. combination therapy and help inform future treatments for enrolled participants.

1.8.4 CELLULAR AND MOLECULAR PROFILING OF SERIAL BIOPSIES

The exploratory research aims of this study are intended to elucidate mechanisms by which metastatic breast cancers develop resistance, either inherent or acquired, to targeted therapies and when and how PARP inhibition sensitizes to immune checkpoint blockade as well as emerging mechanisms to immune checkpoint blockade. Possible resistance mechanisms include: a) tumor intrinsic genomic instability and epigenomic plasticity; b) events extrinsic to the cancers cells, including chemical and mechanical signals from the microenvironments, production of mechanical extracellular matrix barriers and/or changes in vasculature that reduce drug and/or immune cell access; c) nanoscale cancer cell-microenvironment interactions that reduce drug efficacy; d) and a plethora of immune resistance mechanisms such as loss of HLA expression and antigen presentation or immune exhaustion. These mechanisms likely vary between participants and within individual participants and change with time as tumors respond to therapeutic attack.

The overarching aim of these exploratory studies will enable discovery of mechanisms of resistance that arise in individual participants with metastatic breast cancer undergoing treatment with targeted and/or immune therapies. Identified assays and biomarkers can then be further developed and validated in CLIA fashion to guide therapeutic decision making. To address this research objective, a series of exploratory research analytics will be conducted on available blood and tissue specimens (refer to Appendix B for additional information).

1.9 **POTENTIAL RISKS AND BENEFITS**

1.9.1 KNOWN POTENTIAL RISKS

Potential toxicities of the study drug combinations are detailed in Section 9.4. Additional on-study risks to participants are associated with a tumor tissue biopsy, which may include bleeding, infection, pain, and damage to the organ in which the cancer resides.

1.9.1.1 *Immune checkpoint blockade*

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and which may

require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism. Refer to the durvalumab investigator brochure for additional risk information.

1.9.1.2 *Capivasertib*

The safety profile for capivasertib is still emerging. Based on clinical data available to date, the risks associated with capivasertib are as follows:
• Important Identified Risks : Diarrhea, rash, hyperglycemia, hypersensitivity
• Identified Risks : Nausea and vomiting, stomatitis, dry skin, pruritis, decreased appetite, pyrexia, erythemea multiforme. Refer to the capivasertib investigator brochure for additional risk information.

The overlapping toxicities in this study for olaparib and capivasertib are diarrhoea, rash, nausea, vomiting, decreased appetite and stomatitis.

Management of capivasertib related toxicities will be as follows

- Diarrhea, rash- A recommended toxicity management algorithm (see Sections 6.3.4.4 and 6.3.4.6) provided with the protocol will aid consistent and standardised management of capivasertib related diarrhoea and rash across the study.
- Nausea, vomiting, decreased appetite and stomatitis - these can be managed with treatment and interruptions to capivasertib dosing using 'Dose Modifications due to general capivasertib-related toxicities'. These are expected to be evaluated and treated by investigators according to local practice.

1.9.1.3 *Selumetinib*

Possible risks associated with selumetinib include: gastrointestinal events (e.g., diarrhea, nausea, vomiting), dermatological events (e.g., acneiform rash), fatigue, pyrexia, respiratory event (e.g., dyspnea, ILD-type events, including symptoms of shortness of breath, fatigue, cough and/or fever), hypertension, peripheral edema, visual function (e.g., blurred vision, central serous retinopathy/ retinal pigment epithelial detachment), hyperphosphatemia, as well as increases in creatine phosphokinase. Refer to the selumetinib investigator brochure for additional risk information.

1.9.1.4 *Ceralasertib*

The safety profile for ceralasertib is still emerging. Common AEs, defined as those occurring in >10% of patients who received ceralasertib monotherapy include: nausea, fatigue, anemia, thrombocytopenia and vomiting. The most common SAEs include: anemia, decreased appetite, febrile neutropenia, platelet count decreased, and pneumonia. Refer to the ceralasertib investigator brochure for additional risk information.

1.9.2 KNOWN POTENTIAL BENEFITS

Given the lack of treatment options for patients with advanced cancers such as TNBC, the current study may provide access to a new treatment approach not previously available. It

cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

Assess overall response to treatment

2.2 SECONDARY OBJECTIVES

1. Assess participant benefit from treatment
2. Determine the time to disease progression following response to study therapy
3. Determine time to first disease progression or death of participants enrolled on the study
4. Determine survival of participants enrolled on the study
5. Assess safety and tolerability of the proposed therapy

2.3 EXPLORATORY OBJECTIVES

1. To assess a change in quality of life (QOL) as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) in each treatment arm.
2. To assess a change in QOL as measured by Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23) in each treatment arm.
3. Examine response rates depending on tumor characteristics
4. Identify predictive biomarkers of sensitivity to therapy
5. Identify emerging mechanism of resistance to therapy.
6. Determine changes in tumor cells and the tumor microenvironment induced by PARP inhibitors.

3. STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 10*, SAFETY STATISTICAL CONSIDERATIONS for additional information regarding statistical methods used in this study.*

This is a non-comparative, multi-arm, open-label phase II study to assess the efficacy of olaparib in combination with either durvalumab, selumetinib, or capivasertib, or ceralasertib monotherapy for the treatment of patients with metastatic TNBC. Participants must meet all of the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening test(s) not performed routinely in their treatment.

This study will enroll participants with metastatic TNBC (defined as ER <10%, PR <10%, and HER2 non-amplified). Individuals with luminal androgen receptor (LAR) subtype of TNBC, defined as androgen receptor (AR) ≥80% expression by IHC will be excluded from participation. Participants with biopsy-proven TNBC will undergo a pre-treatment biopsy, following which all participants will start a 4-week induction treatment with olaparib (300 mg PO BID). Participants will undergo a repeat on-treatment biopsy 2 weeks (± 7 days) after starting olaparib monotherapy (i.e., Cycle 1, Day 14 ± 7 days). Following the 4-week olaparib induction treatment, participants will then be assigned to one of four treatment arms:

- **Arm 1 –** olaparib (300 mg BID) given from Days 1 to 28, will be administered in combination with durvalumab (1500 mg IV every 4 weeks),
- **Arm 2 –** olaparib (300 mg PO, BID) given from Days 1 to 28, will be administered in combination with selumetinib (BSA dosing per Table 15) for 28 days
- **Arm 3 –** olaparib (300 mg BID) given from Days 1 to 28, will be administered in combination with capivasertib (400 mg PO BID) that is given on a 4 day on/3 day off schedule for 28 days.
- **Arm 4 –**ceralasertib (240 mg PO BID) that is given on Days 1 to 14 of the 28-day treatment cycle.

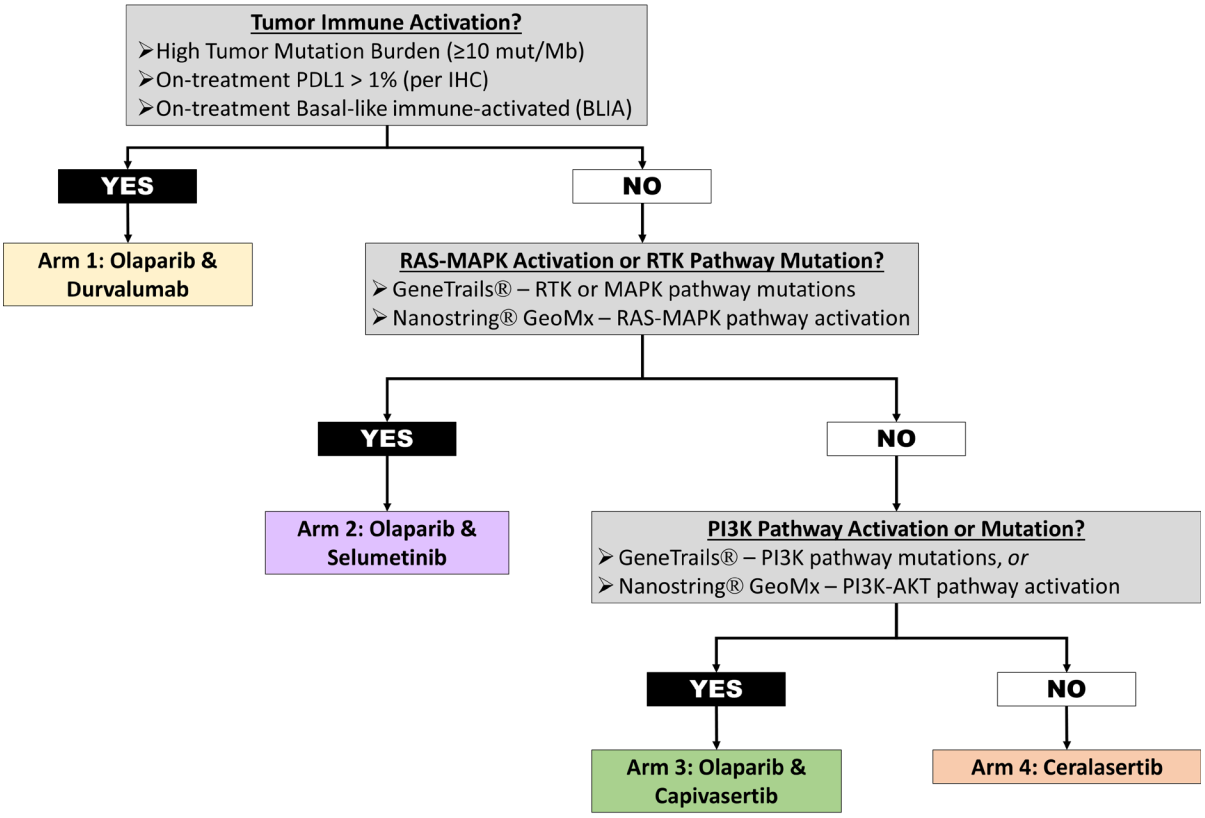
Results obtained from one or more clinically-validated assays (i.e., laboratory-diagnostic test [LDT] or FDA-cleared or approved in vitro diagnostic [IVD] test) using either the pretreatment and/or on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days) may be used to determine treatment assignment based on the decision tree shown in **Figure 2** and the associated criteria described in **Appendix A.** Note that the planned Cycle 2 Day 1 start of olaparib in combination with durvalumab, capivasertib, or selumetinib, or ceralasertib monotherapy treatment may be delayed up to as much as 14 days to allow for the return and analysis of clinical laboratory results.

Following the guidelines described in **Figure 2,** participants with demonstrable immune activation following olaparib monotherapy lead-in will be assigned to Arm 1. Individuals not qualifying for Arm 1 will nex be considered for Arms 2, 3, or 4. Participants with aberrant activation of the RAS-MEK-ERK pathway will be assigned to Arm 2. This is due to evidence that RAS-MEK-ERK pathway activity renders tumors resistant to PARP inhibition, and MEK inhibitors reverse the resistance. Individuals not qualifying for Arm 2 will next be considered based on an altered PI3K-AKT pathway, and if present, then they may be assigned to Arm 3. This is based on our evidence of synergy between PARP and AKT inhibitors in preclinical and clinical studies. Any remaining participants will be assigned to Arm 4, which is considered the default treatment arm for participants that do not meet the specific criteria for any of the other

treatment arms. However, it is expected that most of these patients will have a signature indicative of high replication stress and therefore ceralasertib is an appropriate investigational treatment. Once Arm 1 has completed enrollment, considerations to participant assignment will use decision-tree guidelines beginning with Arm 2, and repeat itself in an iterative process.

Participants with or without *BRCA* mutations are eligible for assignment to treatment Arms 1, 2, 3, or 4. The germline mutational status of *BRCA* among participants at enrollment will be carefully assessed to avoid unwanted overrepresentation or imbalance between treatment arms – as such the total number of *BRCA* mutant participants to any of the study arms should not exceed more than 20% per each stage (i.e., 4 *BRCA* mutant participants/arm, 2 each in stage I and II of each arm).

Figure 2. Decision Tree for Arm Assignment



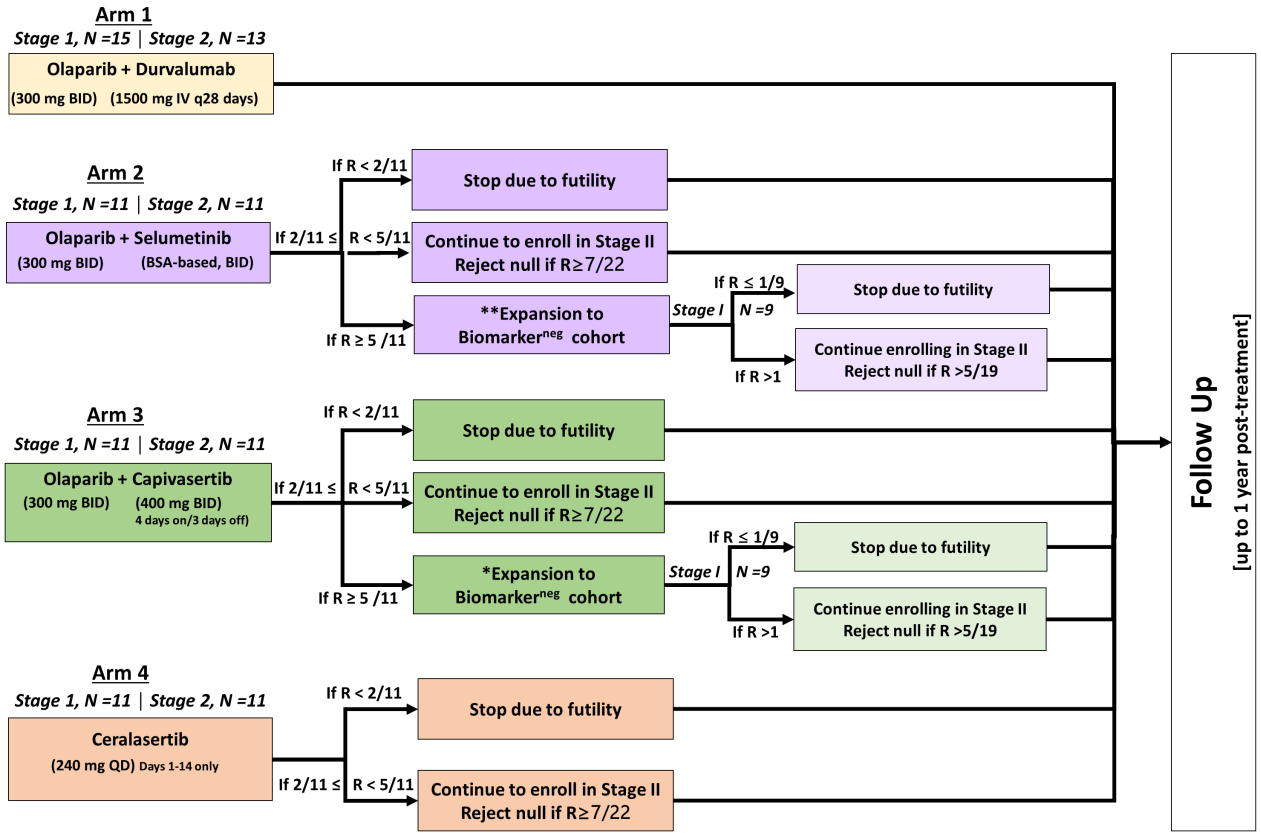
Regardless of treatment assignment, participants are planned to receive 12 cycles of their assigned combination therapy but may continue on therapy beyond the planned 12 cycles in the absence of disease progression or unacceptable toxicity. Participants will also be offered an optional repeat biopsy on disease progression. Up to 132 participants are planned for enrollment to this study.

The trial will be conducted using separate two-stage analyses for each study arm (**Figure 3**). Refer to Section 10.3.1 for additional information pertaining to statistical design.

In Arm 1, up to 15 participants will be enrolled and analyzed in stage I. If there are 2 or fewer responses among these initial participants the study arm will be stopped, otherwise an additional 13 participants will be enrolled and treated in stage II (n = 28) (**Figure 3**).

For Arms 2, 3, and 4, up to 11 participants will be enrolled and treated in stage I of each experimental arm. If, within a study arm, there are 1 or fewer responses among the first 11 participants, then that study arm will be terminated in stage I, otherwise, an additional 11 participants will be accrued to stage II (n = 22 per each study arm) (**Figure 3**).

Figure 3. Study Design for Each Arm



At the time of interim analysis for Arms 2 and 3 only, if there are 5 or more responses among the first 11 participants in stage I of each study arm, then an expansion biomarker negative cohort may be evaluated within that study arm. In such cases, participants enrolled into the study may be assigned to a biomarker negative expansion independent of any pre-defined molecular characteristic described in **Figure 2**. Each study arm that opens a biomarker negative expansion cohort will enroll up to 9 participants in stage I. If 1 or less out of the first 9 participants respond, then the repective study arm's expansion cohort will be terminated, otherwise an additional 10 participants will be accrued to stage II (n = 19 per each study arm that has a biomarker negative expansion cohort) (**Figure 3**). *NOTE:* The biomarker selection arm will continue to enrolling in stage provided interim milestones are met. The biomarker negative expansion cohorts will only open after completion of enrolment of their respective arms (Arm 2 or 3). If, per study design, a biomarker negative arm is warranted, treatment arm assignment will be described in a planned protocol amendment prior to initiation of the expansion biomarker negative arm(s).

3.1.1 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The use of PARP inhibitors in TNBC has been majorly focused on *BRCA*-mutant tumors. This

proposal aims to leverage robust preclinical and early clinical data to expand this benefit to *BRCA*-wildtype TNBC, which represents a poor prognosis population.
The TNBC target population in this study will not include LAR TNBC, defined as those expressing the AR ≥80% by IHC. The rationale for excluding this TNBC subtype stems from our experience across 3 separate clinical trials (NCT03162627, NCT03544125, NCT03801369), which to-date, has revealed that all patients with LAR have demonstrated rapid progression (unpublished). Further, pathway analysis indicates that PARP inhibitors have modest impact on LAR tumors and the tumor microenvironment. LAR tumors do not exhibit immune activity that would be expected to increase response to PARP and PD-L1 inhibitors. Finally, AR expression in breast cancer cell lines induces resistance to PARP inhibitors (unpublished).
The initial biopsy will provide a baseline unperturbed view of systems biology before the initiation of any therapy. The second biopsy will be performed after participants have received monotherapy with olaparib, and before durvalumab is added to their treatment. This approach will allow us to 1) evaluate if olaparib is inhibiting the target adequately; 2) understand the impact of olaparib on the tumor ecosystem; 3) identify emerging mechanisms of primary, adaptive, and acquired resistance to olaparib; and 4) determine effects of PARP inhibitors on the immune system. We will thus be able to learn deeply from each participant biopsy to understand how the tumor ecosystem has adapted to therapeutic stress. This information can then be correlated to participant outcomes to develop biomarkers of sensitivity to therapy and build novel rational combinations aimed at overcoming treatment resistance.

This is a non-comparative study, and the efficacy and safety of the assigned study interventions for each treatment arm (i.e., Arm 1, Arm 2, Arm 3, or Arm 4) will be evaluated independently of one another. For each treatment arm, the primary endpoint is to assess the ORR following completion of on-study treatment with olaparib in combination with durvalumab, capivasertib, or selumetinib, or ceralasertib monotherapy, respectively. Secondary efficacy endpoints will include clinical benefit rate (CBR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) of enrolled participants. Additional secondary endpoints on this study include assessing the safety and tolerability of each combination therapy, in which the severity of on-treatment adverse events will be collected as per CTCAE 5.0. Post-treatment follow-ups will occur for a period of 1-year.

For those assigned to Arm 1, the study aims to achieve a primary endpoint of an ORR of 35% compared to 15% historical control for ICB in TNBC (refer to section 1.2.2). The recently presented Topacio study evaluated a similar combination of Niraparib and Pembrolizumab in metastatic *BRCA*-mutant as well as *BRCA*-wildtype TNBC, with a reported ORR of 28% in that study. The response in *BRCA*-wildtype TNBC was lower and transient. Patients on the Topacio trial could have received up to 2 lines of therapy in the metastatic setting, and almost 40% had received prior platinum therapy. Response to PARP inhibitors has been reported to be lower following platinum therapy, and in our practice clinical trial enrollment, taxanes and eribulin are usually preferred agents for metastatic TNBC prior to using platinum therapy. Additionally, Topacio did not restrict enrolment of LAR TNBC, who we have observed do not benefit from this combination in our experience. We thus expect a significantly smaller proportion of patients to be exposed to platinum prior to enrollment, which will increase the chances of response to our proposed combination, hence the improvement in 20% in ORR that is assumed.

For those assigned to Arms 2-4, the study aims to achieve a primary endpoint of an ORR of 40% compared to 15% historical control. Prior studies show that responses to PARP inhibitor monotherapy, including olaparib, varies widely (**Table 1**). Among patients with advanced/recurrent TNBC or hormone-receptor-positive breast cancer, PARP inhibitor monotherapy achieves responses of 12-47% among those with a BRCA mutation, whereas those with BRCA wild-type breast cancer achieve far lower responses (0-15%).[17,25,26,28,169,170]

Although Arms 2-4 of this trial permit participation of patients with wild-type or mutant BRCA, the latter constitutes only 10-20% of all TNBCs and will represent a small subset of within each treatment arm. As such, establishing a historical response of 15% best captures the reported response rate for PARP inhibitors in this mixed population. Though predominantly comprising patient populations with *BRCA* mutations, prior reports show that the combination of olaparib and paclitaxel or carboplatin can achieve responses between 33-87.5%; and 28% in combination with the PI3K inhibitor, bupralisib.[90,171,172] Building on these studies within our trial, we will test the assumption that a 25% increase in response associated with olaparib in combination with selumetinib, or capivasertib, or ceralasertib monotherapy is clinically meaningful.

3.2 **STUDY ENDPOINTS**

3.2.1 PRIMARY ENDPOINT

Objective	**Endpoint**	**Start**	**End**
1. Assess overall response to treatment	1. ORR olaparib + durvalumab (Arm 1), ORR olaparib + selumetinib (Arm 2), ORR olaparib + capivasertib (Arm 3), ORR ceralasertib (Arm 4)	From completion of Cycle 1	End of treatment [EOT]

3.2.2 SECONDARY ENDPOINTS

Objective	**Endpoint**	**Start**	**End**
1. Assess response to treatment	1. CBR olaparib + durvalumab (Arm 1), CBR olaparib + selumetinib (Arm 2), CBR olaparib + capivasertib (Arm 3), CBR ceralasertib (Arm 4)	From completion of Cycle1	End of Treatment (EOT)
2. Determine the time to disease progression following response to study therapy	2. DOR olaparib + durvalumab (Arm 1), DOR olaparib + selumetinib (Arm 2), DOR olaparib + capivasertib (Arm 3), DOR ceralasertib (Arm 4)	From time of first CR or PR of objective response; from end of cycle 1 for stable disease	End of Treatment (EOT)
3. Determine time to first disease progression or death of participants enrolled on the study	3. PFS olaparib + durvalumab (Arm 1), PFS olaparib + selumetinib (Arm 2), PFS olaparib + capivasertib (Arm 3), PFS ceralasertib (Arm 4)	From completion of cycle 1	Progression or death (any cause) up to 1 year post-treatment
	4. OS olaparib + durvalumab (Arm 1), OS olaparib + selumetinib (Arm 2), OS olaparib + capivasertib (Arm 3), OS ceralasertib (Arm 4)	From completion of cycle 1	Death (any cause) up to 1 year post-treatment
4. Assess safety and tolerability of the proposed therapy	5. Incidence of ≥ Grade 3 toxicities (per CTCAE v5.0) for each proposed treatment arms	Day 1	3 months post-treatment

3.2.3 EXPLORATORY ENDPOINTS

Objective	**Endpoint**	**Start**	**End**
1. To assess a change in QOL as measured by EORTC QLQ-C30 in each treatment arm.	1. Change From Baseline to end of treatment in EORTC QLQ-C30 - Total Score	Day 0 [Baseline]	End of Treatment [EOT]
2. To assess a change in QOL as measured by EORTC QLQBR23	3. Change From Baseline to end of treatment in EORTC QLQBR23 -Total Score	Day 0 [Baseline]	End of Treatment [EOT]

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to understand and the willingness to sign a written informed consent document.
2. Participants are ≥ 18 years old at time of informed consent.
3. Metastatic TNBC, as defined by:
   a. ER and PR negative as defined as ER <10% and PR <10% by immunohistochemistry according to American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for hormone receptor testing
   b. HER2 non-amplified per ASCO/CAP guidelines, defined as:
      i. IHC score 0/1+
      ii. IHC 2+ and in situ hybridization (ISH) non-amplified with a ratio of HER2 to CEP17 <2.0, and if reported, average HER2 gene copy number <4 signals/cells; or
      iii. ISH non-amplified with a ratio of HER2 to CEP17 <2.0, and if reported, average HER2 gene copy number <4 signals/cells
4. Participants with or without germline *BRCA* mutated TNBC are eligible for study participation
5. Participants must have at least one measurable site of disease as defined by RECIST v1.1 (refer to Section 8) that is amenable to biopsy.
6. Prior therapies for metastatic breast cancer
   a. Frontline patients who have not received prior systemic therapy for metastatic breast cancer are eligible.
   b. Patients who have received ≤ 2 prior chemotherapy regimens for metastatic breast cancer are eligible.
7. Participants must have fully recovered from the acute toxic effects of all prior treatment to grade 1 or less, except alopecia which is allowed
8. Participants must have a life expectancy ≥ 16 weeks.
9. Participant must have Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (refer to Appendix C)
10. Participant must consent to undergo a pre-treatment screening biopsy for enrollment and subsequent biomarker analyses.
11. Participants must consent to undergo one mandatory on-study tumor biopsy following a 2-week induction treatment of olaparib. A second on-study biopsy at time of disease progression is optional but not mandatory.
12. Participants must not have received previous treatment with PARP inhibitors, including olaparib
13. Participants must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
    a. Hemoglobin ≥ 10.0 g/dL

b. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

c. Platelet count ≥ 100 x 10^9/L

d. Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

e. Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN

f. Participants must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation or based on a 24-hour urine test:

Estimated creatinine clearance = (140-age [years]) x weight (kg) (x F) serum creatinine (mg/dL) x 72; where F=0.85 for females and F=1 for males.

14. Participants of childbearing potential must have a negative urine or serum pregnancy test within 28 days of study treatment and confirmed on Day 1 prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
15. Participants of childbearing potential agree to use adequate methods of contraception (Appendix D), upon signing of informed consent through:

- 6 months after the last dose with olaparib,
- 3 months after the last dose with durvalumab,
- 1 week after the last dose with selumetinib,
- 1 month after the last dose with capivasertib,
- 1 month after the last dose with ceralasertib.

Participants of childbearing potential are those who are not proven postmenopausal. Postmenopausal is defined as:

- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
- Radiation-induced oophorectomy with last menses >1 year ago
- Chemotherapy-induced menopause with >1 year interval since last menses
- Surgical sterilization (bilateral oophorectomy or hysterectomy)

16. Sperm-producing participants must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant partner or with an individual of childbearing potential. Partners of sperm-producing participants should also use a highly effective form of contraception ([see Appendix D for acceptable methods]) if they are of childbearing potential.

a. Sperm-produding participants assigned to receive capivasertib must use a condom during treatment and for 4 months after the last dose of capivasertib when having sexual intercourse with a pregnant partner or with an individual of childbearing potential.

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Any concurrent anticancer treatment.
   a. Individuals in the follow-up phase of a prior investigational study may participate as long as it has been 4 weeks since last dose of the previous investigational agent or device.
   b. Concurrent use of hormonal therapy for non cancer related conditions (e.g., hormone replacement therapy) is allowed.
2. Participant's with tumors showing androgen receptor (AR) ≥80% by immunohistochemistry are excluded.
3. Other malignancy unless curatively treated with no evidence of disease for ≥5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma. Participants with a personal history of treated early stage breast cancer whose natural history or treatment does not have the potential to interfere with the safety or efficacy endpoints of the trial, per investigator assessment, are eligible.
4. Participants with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.
5. Participant received prior anticancer therapy such as targeted therapies, or systemic chemotherapy or radiation (except for palliative reasons) within the past 3 weeks, or 5 half-lives, whichever is shorter, prior to first day of treatment
6. Participants with known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
   a. Patients with brain metastases may participate provided they do not have symptomatic uncontrolled disease. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. (note: a scan to confirm the absence of brain metastases is not required).
   b. Patients with spinal cord compression are not eligible unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
   c. Patients with carcinomatous meningitis are not eligible.
7. Concomitant use of known strong CYP3A inhibitors (e.g., ketoconazole, posaconazole), or strong CYP3A inducers (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting study intervention treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
8. Major surgery within 4 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
9. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
10. Patients that are immunocompromised, including those with Human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness are not eligible for participation. *Note: HIV-infected participants on effective anti-retroviral therapy with undetectable viral load for ≥6 months are eligible for this trial provided that there is minimal interactions or overlapping toxicity of the antiretroviral therapy with their study intervention.*

Refer to drug-specific exclusion criteria for additional considerations.

11. Patients with known active hepatitis (i.e. Hepatitis B or C). *Refer to drug-specific exclusion criteria for additional considerations.*
    a. Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result.
    b. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible.
    c. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. Those with a positive HCV PCR will be excluded
12. Participants unable to swallow orally administered medication and participants with gastrointestinal disorders likely to interfere with absorption of the study medication
13. Participants with visceral crisis defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease[173].
14. Active infection requiring systemic antibiotic therapy. Participants requiring systemic antibiotics for infection must have completed therapy before treatment is initiated.
15. Participants considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric illness/social situation that prohibits obtaining informed consent.
16. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or participants with congenital long QT syndrome
17. Participants with a history of hypersensitivity reactions to study agent, olaparib, or its excipients.
18. Participant is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
19. Sperm-producing participants are prohibited from donating sperm upon signing of informed consent through:
    - 3 months following last dose with olaparib,
    - 4 months following last dose with capivasertib
    - 6 months following last dose with ceralasertib
20. Involvement in the planning and/or conduct of the study
21. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

4.2.1 DRUG-SPECIFIC EXCLUSION CRITERIA

The following criteria require consideration for participant eligibility to one or more of the available treatment arms. Participant eligibility may be assessed at the time of initial screening or as part of the on-study assignment to a specific treatment arm.

4.2.1.1 *Durvalumab Exclusion Criteria (if being considered for Arm 1)*

1. Participant has received prior immunotherapy with anti-PD-L1, including durvalumab anti-PD-1, anti-CTLA4 or similar drugs in the metastatic setting.
2. Participants may have received prior immunotherapy in the adjuvant setting, provided
   a. No documented disease progression on immunotherapy
   b. Treatment with immunotherapy was >1 year from enrollment on study
3. Participant has evidence of interstitial lung disease or active non-infectious pneumonitis.
4. Major surgery within 2 weeks of starting study treatment and participants must have recovered from any effects of any major surgery Note: Local surgery of isolated lesions for palliative intent is acceptable per investigator discretion.
5. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus**.
   a. Participants with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible.
   b. Participants positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
   c. Those with controlled human immunodeficiency virus (HIV) are eligible, provided that:
      i. baseline CD4+ T-cell count is ≥200 cells/mm^3, and
      ii. HIV plasma viral load is < 60 copies/ml
6. History of active primary immunodeficiency
7. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. The following are exceptions to this criterion:
   a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
   b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
   c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
8. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
   a. Participants with vitiligo or alopecia

b. Participants with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

c. Any chronic skin condition that does not require systemic therapy

d. Participants without active disease in the last 5 years may be included but only after consultation with the study physician

e. Participants with celiac disease controlled by diet alone

9. History of allogenic bone marrow transplant or double umbilical cord blood transplantation
10. Participants must not have received live vaccines within 30 days prior to the first dose of immunotherapy. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed. Patients, if enrolled, should not receive a live vaccine while receiving immunotherapy and up to 30 days after the last dose of immunotherapy
11. Participant has a history of hypersensitivity reactions to study agent, durvalumab, or its excipients.
12. Participants with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Investigator.
13. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Investigator.

4.2.1.2 *Selumetinib Exclusion Criteria (if being considered for Arm 2)*

1. Prior treatment with a MEK, Ras or Raf inhibitor
2. Participants with a history of hypersensitivity reactions to study agent, selumetinib, or its excipients.
3. Current or past history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR) or retinal vein occlusion; or Intraocular pressure (IOP) > 21 mmHg or uncontrolled glaucoma (irrespective of IOP)
4. HIV positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with selumetinib.
5. Inability to swallow selumetinib capsules whole
6. Cardiac conditions as follows:

   a. Uncontrolled hypertension, defined as BP ≥ 150/95 mmHg despite medical therapy

   b. Acute coronary syndrome within 6 months prior to starting treatment

   c. Symptomatic heart failure NYHA Class II-IV, prior or current cardiomyopathy, or severe valvular heart disease (**Appendix E**)

   d. Uncontrolled Angina, defined as Canadian Cardiovascular Society grade II-IV despite medical therapy (**Appendix F**)

7. Prior or current cardiomyopathy including but not limited to the following:

   a. Known hypertrophic cardiomyopathy

b. Known arrhythmogenic right ventricular cardiomyopathy

c. Previous moderate or severe impairment of left ventricular systolic function (LVEF <45% on echocardiography or equivalent on MuGA) even if full recovery has occurred.

d. Baseline Left ventricular ejection fraction (LVEF) below the LLN or <55% measured by echocardiography or institution's LLN for MUGA

e. Severe valvular heart disease

f. Atrial fibrillation with a ventricular rate > 100 bpm on ECG at rest

g. QTcF >450ms or other factors that increase the risk of QT prolongation

4.2.1.3 *Capivasertib Exclusion Criteria (if being considered for Arm 3)*

1. Prior treatment with capivasertib or any of the following:
   a. AKT, PI3K, and/or mTOR inhibitors
2. History of hypersensitivity to active or inactive excipients of capivasertib or drugs with a similar chemical structure or class to capivasertib
3. Clinically significant abnormalities of glucose metabolism as defined by any of the following:
   a. Diabetes mellitus Type I or Type II requiring insulin treatment.
   b. HbA1c ≥8.0% (63.9 mmol/mol).
4. Investigator judgment of 1 or more of the following:
   a. Mean resting corrected QT interval >470 ms, obtained from triplicate ECGs performed at screening.
   b. Medical history significant for arrhythmia (e.g., multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted to enter the study.
   c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia of Grade ≥1, potential for Torsades de Pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relative, history of QT prolongation associated with other medications that required discontinuation of the medication. See for guidance on patients receiving any concomitant medication known to prolong the QT interval.
   d. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (eg, complete left bundle branch block, third degree heart block)
   e. Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure New York Heart Association (NYHA) grade ≥2
   f. Uncontrolled hypotension: systolic BP <90 mmHg and/or diastolic BP <50 mmHg
   g. Cardiac ejection fraction outside institutional range of normal or <50% (whichever is higher) as measured by echocardiogram (or multiple-gated acquisition [MUGA] scan if

an echocardiogram cannot be performed or is inconclusive).

5. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values at screening:
    a. Absolute neutrophil count $<1.5 \times 10^9$/L
    b. Platelet count $<100 \times 10^9$/L
    c. Hemoglobin <9 g/dL (<5.59 mmol/L). [Note: any blood transfusion must be >14 days prior to the determination of a hemoglobin ≥9 g/dL (≥5.59 mmol/L)]
    d. ALT and AST >2.5 × ULN if no demonstrable liver metastases or >5 × ULN in the presence of liver metastases. *Elevated alkaline phosphatase (ALP) is not exclusionary if due to the presence of bone metastasis and liver function is otherwise considered adequate in the investigator's judgement*
    e. Total bilirubin >1.5 × ULN or >3×ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).
    f. Creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); *confirmation of creatinine clearance is only required when creatinine is >1.5 × ULN*
6. Active hepatitis infection, positive hepatitis C antibody, hepatitis B virus surface antigen or hepatitis B virus core antibody, at screening.
    a. Patients who are hepatitis C antibody positive will need to have a negative PCR result before enrolment. Those who are hepatitis C PCR positive will be excluded.
    b. Patients who are hepatitis B virus surface antigen positive or hepatitis B PCR positive will be excluded.
    c. Patients who are anti-HBc antibody positive and who are surface antigen negative will need to have a negative PCR result before enrolment.
7. HIV with a CD4+ T cell count <350 cells/μL or a history of an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the past 12 months.
    a. To ensure that effective anti-retroviral therapy (ART) is tolerated and that toxicities are not confused with investigational drug toxicities, trial participants should be on established ART for at least 4 weeks.
    b. Patients with HIV viral load > 400 copies/mL or those with a history of an AIDS-defining opportunistic infection will be excluded.
    c. Patients with CD4+ T-cell (CD4+) counts < 350 cells/uL will be excluded.
        i. Patients with a higher viral load or lower CD4+ count (< 350 cells/uL) may be considered for eligibility if the patient has a potentially curable malignancy or for interventions in a later stage of development that have demonstrated prior activity with a given cancer.
8. Known to have active tuberculosis infection (clinical evaluation that may include history, physical examination and radiographic findings, or tuberculosis testing in line with institutional practice.
9. Known history of drug or alcohol abuse within 12 months of screening.
10. Refractory nausea and vomiting, malabsorption syndrome, chronic gastrointestinal

diseases, inability to swallow the formulated product or previous significant bowel resection, or other condition that would preclude adequate absorption, distribution, metabolism, or excretion of capivasertib

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

4.2.1.4 *Ceralasertib Exclusion Criteria (if being considered for Arm 4)*

1. Persisting (> 4 weeks) severe pancytopenia due to previous therapy rather than disease, defined as ANC < 0.5 x 10^9/L or platelets < 50 x 10^9/L
2. Prior to study medication, the use of potent inducers or inhibitors of CYP3A are not permitted. For subjects taking any of these drugs (examples provided in Appendix H) the required wash-out period before starting ceralasertib is five half-lives, except for St. John's wort, which is 3 weeks. Subjects should also not received 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. The use of herbal supplements or 'folk remedies' (and medications and foods that significantly modulate CYP3A activity) should be discouraged. Patients should stop using herbal medications 7 days prior to first dose of study treatment.
3. History of hypersensitivity to active or inactive excipients of ceralasertib or drugs with a similar chemical structure or class to ceralasertib.
4. Prior exposure to an ATR inhibitor
5. A diagnosis of ataxia telangiectasia
6. Time from prior treatment as follows:
    a. Cytotoxic chemotherapy, hormonal or non-hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted (a duration of 30 days or 5 half-lives (whichever is longer) is required for patients treated with non-cytotoxic drugs).
    b. The minimum washout period for immunotherapy is 42 days.
    c. Palliative radiotherapy must have been completed 21 or more days before Cycle 1 Day 1 (with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study treatment).
    d. 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.
    e. Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of study agent: patients must have recovered from any effects of any major surgery.
7. Impaired hepatic or renal function as demonstrated by any of the following laboratory values:
    a. Albumin < 33g/L (or outside of local laboratory reference ranges)
    b. ALP > 2.5 x ULN
    c. Creatinine clearance < 50 mL/min, as assessed using thestandard methodology at the

investigating centre (i.e. Cockroft-Gault)

d. Serum creatinine > 1.5 x ULN

e. Hematuria: 3+ on microscopy or dipstick

f. INR ≥ 1.5 or other evidence of impaired hepatic synthesis function

8. Any of the following cardiac criteria currently or within the last 6 months of study entry (by New York Heart Association (NYHA) ≥ Class 2 heart failure, unstable angina, unstable cardiac arrhythmias or reduced LVEF<55%)
9. Any of the following cardiac criteria:
    a. Mean resting corrected QT interval (QTc) >450 msec in males or >470 msec in females , obtained from 3 electrocardiograms (ECGs) 5-10 minutes apart using the Fredericia formula
    b. Conduction abnormality not controlled with pacemaker or medication e.g. complete left bundle branch block, third degree heart block
    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age
    d. Unstable angina pectoris or acute myocardial infarction
    e. Congestive heart failure or known reduced LVEF < 55%
    f. Patients at risk of brain perfusion problems, e.g., medical history of carotid stenosis or pre-syncopal or syncopal episodes, history of TIAs
    g. Patients with relative hypotension (< 100/60 mm Hg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of >20mm Hg
    h. Uncontrolled hypertension (grade 2 or above) requiring clinical intervention

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will be conducted in the US, and participants for this study will primarily be recruited from hematology and oncology practices within OHSU and affiliated community hematology and oncology (CHO) practices; as well as collaborating study sites (e.g., Oregon Oncology Specialists, University of Minnesota, Seattle Cancer Care Alliance). Participants may be identified and referred to this study by their primary treating physician from within OHSU or CHO, collaborating study sites, or from the outside community. Participants may be identified by a member of the participant's treatment team, the PI, research team, or medical and surgical oncology clinics part of OHSU/CHO, or collaborating study sites. As a member of the treatment team, the investigator(s) will screen their participant's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Referral of potential participants to investigator(s) of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of the participant's malignancy.

The investigators(s) may also screen the medical records of potential participants with whom the investigator does not have a treatment relationship. This will be done for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these potential individuals regarding the possibility of

participating in the study. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

4.3.1 ACCRUAL ESTIMATES

This is a multi-arm, phase II study with a target enrollment of up to 132 participants.

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial, or ethnic origin. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited.

The projected gender, racial, and ethnic composition of the study will comprise females because breast cancer largely or mostly affects this population. The projected racial and ethnic composition of the female study participants will represent that of the state of Oregon, as well as that of the states of any participating collaborating study site.

4.3.2 INCLUSION OF CHILDREN

This protocol does not include children as the number of children with this type of cancer is limited.

4.4 **REGISTRATION PROCEDURES**

4.4.1 PARTICIPANT REGISTRATION

4.4.1.1 *Local Registration*

Participants will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care. Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (CRMS, e.g., eCRIS). At a minimum, registration of OHSU participants will include:

- Signed copies of the most recently Institutional Review Board (IRB)-approved, informed consent form and HIPAA authorization.
- Investigator validation (signature and date) on participant's inclusion and exclusion criteria

4.4.1.2 *Multicenter Registration*

The OHSU coordinating center study team will manage the participant registration process. Investigators, or study team designee, at participating sites will identify eligible participants and send source documents that support eligibility to OHSU for review and verification before the participating site may enroll and treat the participant.

The OHSU coordinating center team is responsible for verifying completeness of documents, entering registration information into the Knight CRMS, and assigning a study number/identifier for each individual participant. The OHSU coordinating center will send an email to the participating site to indicate whether or not a participant is eligible and will assign a participant number/identifier.

Registration at a participating research site will, at a minimum, include signed copies of the most

recent local IRB-approved, informed consent form and HIPAA authorization. Upon consent, the participating study site must notify the OHSU coordinating site via breastclinicaltrials@ohsu.edu to register participants and obtain a participant identification number. The participant identification numbers assigned by OHSU will begin with the site number and end with a sequential number.

4.5 PARTICIPANT SCREENING AND ENROLLMENT

In order to participate in this study, signed informed consent must be obtained from the participant. The current IRB-approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

Screening will begin once the participant has provided written informed consent to participate in the study and ends on Day 1 of the study. All screening and baseline evaluations will be performed during the screening phase (i.e., up to 28 days) before treatment when the study medication is initiated). Day 1 of the clinical trial will be when participants receive the first dose of on-study drug agent(s). Total accrual of all participants is anticipated to take a total of 30 months.

4.6 PARTICIPANT WITHDRAWAL OR DISCONTINUATION

Participants are free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. If a participant no longer wants to receive the on-study investigational drug regimen but is willing to participate in follow-up, the participant's request should be honored, if possible. No research biopsies will be performed. If a biopsy is performed for other purposes, the participant's permission will be sought to use excess tissue for banking and to support future unspecified research. An individual participant will not receive any further investigational product if any of the following occur in the participant in question:

- Withdrawal of consent or lost to follow-up.
- Adverse event that, in the opinion of the investigator, contraindicates further dosing.
- Participant is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- Pregnancy or intent to become pregnant.
- Grade ≥ 3 infusion reaction.
- Participant noncompliance that, in the opinion of the investigator, warrants withdrawal; e.g., refusal to adhere to scheduled visits.
- Initiation of alternative anticancer therapy including another investigational agent
- Requirement for concomitant use of a medication that is contraindicated (refer to Sections 6.6 and 6.7)

If a participant withdraws consent, they will be specifically asked if they are withdrawing consent to:

- all further participation in the study including any further follow up (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any biological samples

No further participant contact should be made if the participant withdraws consent for participation in the study (including further follow-up). Information about the reason(s) for discontinuation and collection of any new or ongoing adverse events (AEs) should be collected at the time the participant withdraws consent.

For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 7.14.

4.6.1 HANDLING PARTICIPANT WITHDRAWAL AND DISCONTINUATION

Participants enrolled in this study that withdraws prior to initiating on-study treatment will be replaced. Participants that receive olaparib, but do not undergo planned treatment with the combination therapy (i.e., olaparib and durvalumab) will be replaced.

4.7 **OFF-STUDY CRITERIA**

Criteria that can take a participant off-study include:
- Participant requests to be withdrawn from study without further follow-up,
- Completed study follow-up period,
- Progression of disease,
- Death,
- Screen failure,
- Investigator's discretion

4.7.1 SCREEN FAILURES

Any participant that has signed the consent form (for either screening or study participation) but does not meet the study eligibility criteria, or meets study eligibility criteria but terminates their participation prior to receiving study treatment, will be considered a screen failure. The reason for screen failure should be captured in the database for each participant failing to meet the eligibility criteria.

4.8 **STUDY DISCONTINUATION**

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Sponsor, IRB, and other regulatory agencies (as required). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Reasons for terminating the study (or a single arm on the study) may include the following:
- Incidence or severity of adverse events, in this or other studies, indicates a potential health hazard to participants.
- Demonstration of efficacy that would warrant stopping.
- Data that are not sufficiently complete and/or evaluable.
- Investigator(s) do not adhere to the study protocol, or applicable regulatory guidelines in conducting the study.
- Participant enrollment is unsatisfactory.
- Submission of knowingly false information from the study site to regulatory authorities.
- Upon instruction by local or other regulatory, or oversight authority.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor, IRB and/or FDA.

5. INVESTIGATIONAL PRODUCT

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in the Adverse Events List (Section 9.4).

5.1 OLAPARIB

Olaparib (Lynparza®) is an inhibitor of poly (ADP-ribose) polymerases (PARP), which include PARP1, PARP2, and PARP3. The PARP enzymes are involved in maintaining normal cellular homeostasis. Refer to the olaparib investigator brochure for additional details.

5.1.1 ACQUISITION

The Investigational Products Supply section of AstraZeneca will supply olaparib tablets to the investigator. Following submission and approval of the required regulatory documents, a supply of olaparib may be ordered from AstraZeneca by completing a Drug Request Form.

Allow 4 business days for shipment of drug from receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. There will be no weekend or holiday delivery of drugs.

5.1.1.1 *Multicenter Acquisition*

Following participant registration, notify OHSU Research Pharmacy Services (RPS) at invdrugs@ohsu.edu to obtain drug. Maintenance of drug accountability records is required for Olaparib. The investigator, or a responsible party designated by the investigator, will maintain a careful record of the receipt, storage, disposition, and return of all drugs supplied for this study.

5.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Olaparib is a crystalline solid. Tablets are available for oral administration in 100 mg or 150 mg concentrations. Inactive ingredients in the tablet core are: copovidone, mannitol, colloidal silicon dioxide, and sodium stearyl fumarate. The olaparib tablet coating consists of hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow, and ferrosoferric oxide (150 mg tablet only).

a) Olaparib tablets (150mg) are green to green/grey, oval bi-convex, film-coated, and embossed with “OP150”. Olaparib 150mg is available in bottles of 60 or 120 tablets.

b) Olaparib tablets (100mg) are yellow to dark yellow, oval bi-convex, film-coated, and embossed with “OP100”. Olaparib 100mg is available in bottles of 60 or 120 tablets.

5.1.3 PRODUCT STORAGE AND STABILITY

Store at 15°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59F to 86°F). Store in original bottle to protect from moisture.

5.1.4 COMPATIBILITY

Olaparib shows pH-independent low solubility of approximately 0.1 mg/ml across the physiological pH range.

5.1.5 HANDLING

National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package.

5.1.6 PREPARATION

None

5.1.7 ADMINISTRATION

Olaparib will be dispensed by the OHSU RPS or respective pharmacy services for each participating subsite. Olaparib (300mg) is to be administered orally twice daily, with or without food, for a total daily dose of 600 mg. The 100 mg tablet is available for dose reductions.

5.1.8 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

Olaparib tablets should be taken at the same time each day, approximately 12 hours apart, with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any participant enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken, and the participant should take their allotted dose at the next scheduled time. It is prohibited to consume grapefruit juice while on olaparib therapy.

5.2 **DURVALUMAB (MEDI4736)**

Durvalumab (IMFINZI™, MEDI4736) is a human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the interaction of PD-L1 with PD-1 on T-cells and CD80 on immune cells. Refer to the durvalumab investigator brochure for additional information.

5.2.1 ACQUISITION

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab (MEDI4736) to the investigator as a 500-mg vial solution for infusion after dilution. Following submission and approval of the required regulatory documents, a supply of durvalumab may be ordered from AstraZeneca/MedImmune by completing a Drug Request Form.

Allow 4 business days for shipment of drug from receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. There will be no weekend or holiday delivery of drugs.

5.2.1.1 *Multicenter Acquisition*

Following participant registration, notify OHSU RPS at invdrugs@ohsu.edu to obtain drug. Maintenance of drug accountability records is required for Olaparib. The investigator, or a responsible party designated by the investigator, will maintain a careful record of the receipt, storage, disposition, and return of all drugs supplied for this study.

5.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Durvalumab (MEDI4736) will be supplied as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

5.2.3 COMPATIBILITY

Do not infuse other drugs via the same IV line as durvalumab

5.2.4 HANDLING

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the study agent in a self-contained and protective environment. Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

5.2.5 PREPARATION OF DURVALUMAB DOSES FOR ADMINISTRATION WITH AN IV BAG

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C – 8°C (36°F – 46°F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours (that is, the individual storage time limits are not additive).

A dose of 1500mg (for participants >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (i.e., 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. Patients with ≤ 30kg weight should be dosed by weight 20mg/kg durvalumab Q4W.

5.2.6 ADMINISTRATION

Standard infusion time 1 hour, and modifications and/or interruptions to infusion time are allowed per local practice and institutional guidelines. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Administer infusion solution intravenously through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 µm in-line filter. Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not

flushed.

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

5.2.7 SPECIAL CONSIDERATION FOR ADMINISTRATION

Durvalumab must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

5.2.7.1 *Monitoring Durvalumab Dose Administration*

Participants who have an infusion-related reaction will be monitored before, during, and after the infusion with the assessment of vital signs at times specified in the Schedule of Events. In such cases, participants are monitored (e.g., pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit participants to an intensive care unit if necessary.

Please refer to 6.5.13 for the management of participants who experience an infusion reaction.

5.3 **CAPIVASERTIB**

Capivasertib is a potent, selective inhibitor of the kinase activity of all 3 AKT isoforms that is under clinical development for the treatment for solid and hematological malignancies. Refer to the capivasertib investigator brochure for additional information.

5.3.1 ACQUISITION

The Investigational Products Supply section of AstraZeneca will supply capivasertib tablets to the investigator. Following submission and approval of the required regulatory documents, a supply of capivasertib may be ordered from AstraZeneca by completing a Drug Request Form.

Allow 4 business days for shipment of drug from receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. There will be no weekend or holiday delivery of drugs.

5.3.1.1 *Multicenter Acquisition*

Following participant registration, notify OHSU RPS at invdrugs@ohsu.edu to obtain drug. Maintenance of drug accountability records is required for capivasertib. The investigator, or a responsible party designated by the investigator, will maintain a careful record of the receipt, storage, disposition, and return of all drugs supplied for this study.

5.3.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The drug product is available for oral administration as beige film-coated tablets containing 160 mg (round, 10 mm) or 200 mg (caplet shaped, 14.5 x 7.25 mm) of capivasertib. The film-coated tablets contain capivasertib, microcrystalline cellulose, dibasic calcium phosphate, croscarmellose sodium, and magnesium stearate.

5.3.3 PRODUCT STORAGE AND STABILITY

The product should be stored in the pack provided and used according to the instructions on the label.

5.3.4 HANDLING

National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package.

5.3.5 PREPARATION

None.

5.3.6 ADMINISTRATION

Capivasertib will be dispensed by the OHSU RPS or respective pharmacy services for each participating subsite. Capivasertib (400 mg) is to be administered orally twice daily, without food, for a total daily dose of 800 mg for 4 days, followed by a 3-day break in treatment.

5.3.7 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

Capivasertib tablets should be taken at the same time each day, approximately 12 hours apart, with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Capivasertib tablets should be taken without food, with participants preferably fasting approximately 2 hours before dosing and up to 1 hour after dosing. If vomiting occurs shortly after the capivasertib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any participant enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken, and the participant should take their allotted dose at the next scheduled time.

5.4 **SELUMETINIB**

Selumetinib is a potent inhibitor of MEK1/2. Refer to the selumetinib investigator brochure for additional information.

5.4.1 ACQUISITION

AstraZeneca will supply selumetinib capsules to the investigator. Following submission and approval of the required regulatory documents, a supply of selumetinib may be ordered from AstraZeneca by completing a Drug Request Form.

Allow 4 business days for shipment of drug from receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. There will be no weekend or holiday delivery of drugs.

5.4.1.1 *Multicenter Acquisition*

Following participant registration, notify OHSU RPS at invdrugs@ohsu.edu to obtain drug. Maintenance of drug accountability records is required for selumetinib. The investigator, or a responsible party designated by the investigator, will maintain a careful record of the receipt, storage, disposition, and return of all drugs supplied for this study.

5.4.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The drug product is available as a capsule for oral administration. The drug product may be provided in 10 mg or 25 mg capsule forms. The capsules contain selumetinib and Vitamin E polyethylene glycol succinate. The 10 mg capsule shell contains: hypromellose, carrageenan, potassium chloride, titanium dioxide, carnauba wax, and purified water. The 10 mg capsule printing ink contains: shellac, iron oxide black, propylene glycol, and ammonium hydroxide. The 25 mg capsule shell contains: hypromellose, carrageenan, potassium chloride, titanium dioxide, FD&C blue 2, ferric oxide yellow, purified water, carnauba wax and/or corn starch. The 25 mg printing ink contains: ferric oxide red, ferric oxide yellow, FD&C Blue 2 aluminum lake, carnauba wax, shellac, glyceryl monooleate.

5.4.3 PRODUCT STORAGE AND STABILITY

The capsules should be stored in their original packaging until use. For further information, investigators should refer to the investigational product label.

5.4.4 HANDLING

National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact capsules or administering from a unit-dose package.

5.4.5 PREPARATION

None

5.4.6 ADMINISTRATION

Selumetinib will be dispensed by the OHSU RPS or respective pharmacy services for each participating subsite. Selumetinib is to be administered orally twice daily, without food, that is based on body surface area (BSA) dosing per Table 15.

5.4.7 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

Selumetinib capsules should be taken at the same time each day, approximately 12 hours apart, with one glass of water. The capsules should be swallowed whole and not chewed, crushed, dissolved, or opened. Selumetinib capsules should be taken without food, with participants preferably fasting approximately 2 hours before dosing and up to 1 hour after dosing. If vomiting occurs shortly after the selumetinib capsules are swallowed, no additional dose should be taken, but instead, continue with the next scheduled dose. Should any

participant enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the capsules), the participant will be allowed to take the scheduled dose up to a maximum of 6 hours after that scheduled dose time. If greater than 6 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.

5.5 **CERALASERTIB**

Ceralasertib is a potent, selective inhibitor of the serine (Ser)/threonine (Thr)-specific protein kinase, ATR, as well as good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. Refer to the ceralasertib investigator brochure for additional information.

5.5.1 ACQUISITION

AstraZeneca will supply ceralasertib tablets to the investigator. Following submission and approval of the required regulatory documents, a supply of ceralasertib may be ordered from AstraZeneca by completing a Drug Request Form.

Allow **8 weeks** for shipment of drug from receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. There will be no weekend or holiday delivery of drugs.

5.5.1.1 *Multicenter Acquisition*

Following participant registration, notify OHSU RPS at invdrugs@ohsu.edu to obtain drug. Maintenance of drug accountability records is required for ceralasertib. The investigator, or a responsible party designated by the investigator, will maintain a careful record of the receipt, storage, disposition, and return of all drugs supplied for this study.

5.5.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Ceralasertib is a crystalline powder that is presented as film-coated tablets containing 20 mg or 80 mg of the drug product. Ceralasertib coated tablets contain a blend of ceralasertib, mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and silicon dioxide.

5.5.3 PRODUCT STORAGE AND STABILITY

The product should be stored in the pack provided and used according to the instructions on the label.

5.5.4 COMPATIBILITY

Ceralasertib displays classic pH-dependent solubility behavior in the intestinal pH range, with a solubility of 26.6 mg/mL at pH 2.5 and 0.49 mg/mL at pH 6.5.

5.5.5 HANDLING

National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets .

5.5.6 PREPARATION

None

5.5.7 ADMINISTRATION

Ceralasertib will be dispensed by the OHSU RPS or respective pharmacy services for each participating subsite. Ceralasertib (240 mg) is to be administered orally twice daily for days 1-14 of every 28 day cycle.

5.5.8 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

Ceralasertib tablets should be taken at approximately the same time each day, with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Ceralasertib tablets should be taken after fasting for 2 hours before dosing and for an additional 1 hour after the dose has been administered. If vomiting occurs shortly after the ceralasertib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any participant enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken, and the participant should take their allotted dose at the next scheduled time. It is prohibited to consume grapefruit juice while on ceralasertib therapy.

5.6 **ACCOUNTABILITY (ALL INVESTIGATIONAL PRODUCTS)**

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The Investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the site.
- Use by each participant including pill/unit counts from each supply dispensed.
- Return of investigational product to the Investigator or designee.
- Destruction or return of investigational product for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The Investigator

will also maintain records adequately documenting that the participants were provided the correct study medication specified. Completed accountability records will be archived by the

5.7 DESTRUCTION AND RETURN (ALL INVESTIGATIONAL PRODUCTS)

At the completion of the study, the Investigator or designee will oversee the destruction of study agents per local institutional guidelines.

6. TREATMENT PLAN

6.1 DOSAGE AND ADMINISTRATION

Treatment will be administered on an *out-patient* basis, with 28 consecutive days defined as a treatment cycle. Reported adverse events and potential risks are described in Section 9.4, Adverse Event List(s). Appropriate dose modifications are described in Section 6.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Table 3. Regimen Description

Agent	***Premedication ; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Olaparib		300 mg	PO	*BID*	28 days
Durvalumab	1-2 mg/kg/day prednisone or equivalent	1500 mg	IV over 1hr*	*Q4wk*	28 days
Capivasertib		400 mg	PO	*Intermittent dosing of 4 days BID on,3 days off*	28 days
Selumetinib		BSA dosing per Table 15	PO	*BID*	28 days
Ceralasertib		240 mg	PO	*BID for days 1 to 14*	28 days

6.1.1 CYCLE 1 – LEAD IN MONOTHERAPY REGIMEN

Participants will receive olaparib (300 mg) orally, twice a day (i.e., every 12 hours) starting on Day 1 for a total of 28 days (i.e., 1 cycle). Halfway through this 4-week induction treatment period, participants will undergo an on-study tumor biopsy (i.e., Cycle 1, Day 14 ± 7 days). After the induction treatment period, participants will receive olaparib in combination with the assigned medication for each treatment arm or ceralasertib monotherapy (Section 6.1.2).

6.1.2 CYCLE 2 TO CYCLE 13 – COMBINATION THERAPIES AND CERALASERTIB MONOTHERAPY

Based on selection criteria guidelines described in Appendix A, participants will be assigned to one of 4 treatment arms comprising either olaparib (300 mg PO BID) administered in combination with durvalumab, capivasertib, or selumetinib, or ceralasertib monotherapy.

6.1.2.1 *Arm 1 – Olaparib and Durvalumab*

Olaparib (300 mg, PO, BID) will be administered at the same specified dose and timing for another 12 cycles (i.e., for a total of 13 on-study treatment cycles). Starting on Cycle 2, participants in Arm 1 will concomitantly receive durvalumab (1500 mg IV) on Day 1 of each 28-day cycle for a total of 12 cycles.

6.1.2.2 *Arm 2 – Olaparib and Selumetinib*

Olaparib (300 mg, PO, BID) will be administered at the same specified dose and timing for another 12 cycles (i.e., for a total of 13 on-study treatment cycles). Starting on Cycle 2,

participants will concomitantly receive selumetinib (BSA dosing per Table 15) to be administered continuously for 28 days, for a total of 12 cycles.

6.1.2.3 *Arm 3 – Olaparib and Capivasertib*

Olaparib (300 mg, PO, BID) will be administered at the same specified dose and timing for another 12 cycles (i.e., for a total of 13 on-study treatment cycles). Starting on Cycle 2, participants will concomitantly receive capivasertib (400 mg PO, BID) for 4 days, followed by a 3-day break in treatment. This alternating treatment regimen will be repeated throughout each 28-day cycle for a total of 12 cycles.

6.1.2.4 *Arm 4 – Ceralasertib monotherapy*

Starting on Cycle 2, participants will receive ceralasertib (240 mg PO BID) to be administered on Day 1 through 14 of each 28-day cycle, for a total of 12 cycles.

Participants in any of the available treatment arms may continue to receive their assigned therapy beyond the planned 13 cycles in the absence of disease progression or unacceptable toxicity. Participants in Arm 1 suspected of pseudoprogrsison could be treated beyond suspected disease progression at the investigator's discretion if they are deriving apparent clinical benefit and tolerating treatment. Participants with confirmed disease progression (per RECIST v1.1 for Arms 2-4, or irRECIST for Arm 1) will be offered physician's choice therapy per institutional guidelines. In this case, participants are considered off-protocol directed therapy, but be followed for disease status and survival outcomes.

6.2 **DOSING DELAYS**

In general, dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (i.e., elective surgery, unrelated medical events, vacation, and holidays) not related to study therapy. Participants should be placed back on study therapy within 4 weeks of the scheduled interruption unless otherwise discussed with the investigator. The reason for interruption should be documented in the participant's study record.

6.2.1 OLAPARIB

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

6.2.2 DURVALUMAB

Durvalumab dosing can be delayed up to 3 cycles, or 12 weeks, due to toxicity, for up to two occurrences. In the event of a third occurrence of a toxicity requiring a dosing delay, study therapy will be permanently discontinued.

6.2.3 CAPIVASERTIB

Treatment with capivasertib may be temporarily interrupted for toxicities, as described in Section

6.3.4.

6.2.4 SELUMETINIB

Any toxicity observed during the course of the study may be managed by an interruption or dose reductions of selumetinib described in Section 6.3.5.

6.2.5 CERALASERTIB

Any toxicity observed during the course of the study may be managed by an interruption or dose reductions of ceralasertib described in Section 6.3.6.

6.3 DOSE MODIFICATION GUIDELINES

As applicable, and per the medical judgement of the treating physician, cases of overlapping hematological and non-hematological toxicities for all the olaparib treatment combinations (i.e., Arms 1, 2, and 3), may be managed by dose modifications to olaparib and/or the respectively assigned combination study agent (i.e., durvalumab, selumetinib, or capivasertib).

6.3.1 MANAGEMENT OF OLAPARIB-RELATED TOXICITIES

Table 4. Dose reductions for olaparib treatment

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

Table 5. Dose reduction for olaparib treatment if participant develops moderate renal impairment

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

Table 6. Dose reductions for study treatment if participant has to start taking a strong or moderate CYP3A inhibitor

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

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided (see Section 6.6).

When dose reduction is necessary, participants will take one 150 mg tablet and one 100 mg tablet twice daily or two x 100 mg tablet twice daily, or one 150 mg tablet twice daily or one 100 mg tablet twice daily (see Section 6.6).

Any toxicity observed during the course of the study could be managed by an interruption of the study drug treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must

be informed. Olaparib can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reductions are permitted, and the participant's on-study treatment should be discontinued. Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors (refer to Section 6.6.1).

6.3.1.1 *Management of hematological toxicity – Anemia*

Table 7. Management of anemia	
Hemoglobin (Hb)	**Action to be taken**
Hb < 10 ***but*** **≥ 8 g/dl** **(CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. **First occurrence:** Physician judgment to continue olaparib with supportive treatment (e.g., transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl. **Subsequent occurrences:** If repeat Hb**< 10** ***but*** **≥ 9 g/dl** investigator judgement to continue *olaparib* with supportive treatment (e.g., transfusion) *or* dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If Hb**< 9** ***but*** **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).
Hb < 8 g/dl **(CTCAE Grade 3)**	Give appropriate supportive treatment (e.g., transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery, dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

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

guidance later in this section for the management of this.

6.3.1.2 *Management of hematological toxicity – neutropenia, leukopenia and thrombocytopenia*

Table 8. Management of neutropenia, leukopenia and thrombocytopenia	
Toxicity	**Olaparib dose adjustment**
CTCAE Grade 1-2	Investigator judgment to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Adverse events of neutropenia and leukopenia should be managed as deemed appropriate by the investigator or physician with close follow up and interruption of program drug if CTCAE grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a participant develops febrile neutropenia, olaparib should be stopped, and appropriate management including G-CSF should be given according to institutional guidelines.

Note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of olaparib unless absolutely necessary.

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

In cases where participants develop prolonged hematological toxicity (≥2 week interruption or delay in treatment due to CTCAE grade 3 or worse), refer to Section 6.3.1.3.

6.3.1.3 *Management of prolonged hematological toxicities*

If a participant develops prolonged hematological toxicity such as:

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

Monitor weekly differential blood counts, including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the participant should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to institutional guidelines. Olaparib should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption.

The development of a confirmed myelodysplastic syndrome or other clonal blood disorder

should be reported as an SAE and full reports must be provided by the investigator to sponsor and AstraZeneca Patient Safety. Olaparib should be discontinued in the event of a participant having a confirmed diagnosis of myelodysplastic syndrome and/or acute myeloid leukemia.

6.3.1.4 *Management of non-hematological toxicity*

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

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

6.3.1.5 *Management of new or worsening pulmonary symptoms*

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in olaparib dosing is recommended, and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib can be restarted, if deemed appropriate by the site investigator. Identification of significant pulmonary abnormalities need to be discussed with the site investigator.

6.3.1.6 *Management of Nausea and Vomiting*

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent, and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

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

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

6.3.1.7 *Interruptions for intercurrent non-toxicity related events*

Olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart on-study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be

discussed with the investigator.

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

Olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery, on-study treatment can be restarted when the wound has healed. No stoppage of treatment is required for any needle biopsy procedure[174].

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

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

6.3.2 RENAL IMPAIRMENT

If subsequent to study entry and while still on study therapy, a participant's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly. A dose reduction is recommended for participants who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.
Olaparib has not been studied in participants with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if participants develop severe impairment or end-stage disease, it is recommended that olaparib be discontinued.

6.3.3 MANAGEMENT OF DURVALUMAB-RELATED TOXICITIES

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the **separately provided durvalumab Toxicity Management Guidelines (TMG).**

Participants should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-mediated adverse events (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune-related.

Refer to the separately provided TMG for general dose modification guidelines associated with immune-related reactions. In general, based on the severity of the adverse reactions, durvalumab should be withheld and corticosteroids administered. Increasing the dose of corticosteroids and/or using other systemic immunosuppressants may be warranted (at the discretion of the treating physician) if there is worsening or no improvement. Upon improvement to ≤Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Refer to **Table 9** for the management of non-immune-mediated adverse reactions.

Table 9. Recommended Non–Immune-Mediated Reactions treatment modifications*		
Severity Grade of Event (NCI CTCAE v. 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

6.3.3.1 *Infusion-related reaction*

Participants who have an infusion-related reaction will be monitored before, during, and after the infusion with the assessment of vital signs at times specified in Section 7.14, Schedule of Events. Participants are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). Refer to separately provided TMG for general dose modification guidelines associated with infusion-related reactions.

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For participants with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.

If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued.

The standard infusion time is one hour; however, if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit participants to an intensive care unit if necessary.

6.3.4 MANAGEMENT OF CAPIVASERTIB-RELATED TOXICITIES

6.3.4.1 *Dose Modifications due to general capivasertib-related toxicities*

When intervention-related toxicities are observed, the investigator will decide, on a case by case basis, whether dose discontinuation, interruption, delay or reduction of therapy is most appropriate.

Appropriate and optimal intervention of the toxicity is assumed prior to considering dose modifications. The study physician may be consulted prior to discontinuation of study drug due to toxicities. The following should be considered:

- Severity of study intervention related toxicity and the number of concurrent adverse events
- Likely causality to study agents based on previous clinical experience and published safety data (refer to the capivasertib and olaparib IBs, respectively)

Intervention with capivasertib should be temporarily interrupted for any intolerable AE regardless of grade or for any AE grade ≥3, where the investigator considers the AE of concern to be specifically associated with capivasertib (not attributable to the disease under investigation or olaparib). A maximum of 2 dose reduction steps are permitted (**Table 10**). If, after the second dose reduction treatment is not tolerated, no further dose reduction is allowed, and study treatment should be discontinued. Dose modification guidelines for capivasertib-related toxicities are shown in **Table 11**.

Table 10. Dose reductions for capivasertib treatment

Initial Dose	**Following re-challenge post interruption:**	
	Dose reduction 1	**Dose reduction 2**
400 mg twice daily (4 days on/3 days off)	320 mg twice daily (4 days on/ 3 days off)	200 mg twice daily (4 days on/ 3 days off)

Table 11. Dose modifications for general capivasertib-related toxicities

Severity Grade of Event (NCI CTCAE v. 5.0)	**Toxicity Management**
Grade 1 or 2 clinically significant • Resolves to baseline or clinically tolerable within 21 days of onset	Hold dosing and follow algorithm below, depending on outcome • Resume dosing at same dose or one reduced dose level as clinically appropriate (**Table 10**)

Table 11. Dose modifications for general capivasertib-related toxicities	
Severity Grade of Event (NCI CTCAE v. 5.0)	**Toxicity Management**
• Does not resolvea within 21 days of onset	• Discontinue study drug and observe patient until resolution
Grade ≥3	Hold dosing and follow algorithm bellow, depending on outcome
• Grade ≥3 toxicity for ≤21 days and resolves to ≤Grade 2or baseline within 21 days of onset	• Resume dosing at same dose or one reduced dose level as clinically appropriate (**Table 10**)
• Grade ≥3 toxicity for >21 days	• Discontinue study drug and observe patient until resolution

6.3.4.2 *Hyperglycemia*

These are general recommendations; therefore, due consideration should be given to baseline values and fasting conditions (and time since food if applicable) when interpreting glucose results. In diabetic patients, it may be beneficial to rule out concomitant aetiologies that could be associated with hyperglycaemia (e.g. infections, dehydration, vascular events, glucocorticoids). Participants should be made aware of symptoms of hyperglycaemia (eg, polydipsia and polyuria). Dose modification guidelines for capivasertib-related hyperglycemia are shown in **Table 12**.

In addition, for all grades, patients may receive education on lifestyle changes (eg, a diabetic diet) and consider beginning home glucose monitoring (eg, fasting self-blood glucose monitoring [SBGM] once-daily) at the discretion of the investigator. If glucose home monitoring is instituted, the capivasertib treatment decision should be based on the morning fasting glucose value obtained prior to the dose of capivasertib.

It is recommended that approaches to the management of capivasertib-induced hyperglycaemia include advice from a diabetologist where appropriate (eg, diabetic patients). Metformin is currently the preferred oral antidiabetic recommended for the management of hyperglycaemia occurring in patients participating in studies of capivasertib (see below for further guidance). If a second agent is required, consideration should be given to the intermittent schedule of capivasertib and the pattern of glucose changes (eg. sulphonylureas should be avoided due to their risk of hypoglycaemia secondary to their mechanism of action).

Table 12. Dose modifications for capivasertib-related hyperglycemia	
NCI CTCAE v5 Toxicity Grade	**Management**
Grade 1 Abnormal glucose above baseline with no medical intervention	Maintain same capivasertib dose level.

Table 12. Dose modifications for capivasertib-related hyperglycemia	
NCI CTCAE v5 Toxicity Grade	**Management**
Grade 2 Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Asymptomatic • Maintain same capivasertib dose level. • Treatment as per local guidelines, consider the use of oral antidiabetic (eg, metformin) on capivasertib dosing days [see further guidance on choice of antidiabetic agents on text above and below the table]. Symptomatic (Appropriate clinical management as per local guidelines) • Interrupt capivasertib until resolution of symptoms and fasting blood glucose is ≤ 160 mg/dL or ≤8.9 mmol/L (treatment can be interrupt up to 21 days) • Restart at same dose level maintaining appropriate antidiabetic treatment (eg addition of/higher dose of oral metformin) • Consider consult with the diabetologist
Grade 3 Insulin therapy initiated; hospitalization indicated	Hold capivasertib up to 21 days, until resolution of symptoms.Consult with diabetologist. • If fasting blood glucose decreases to ≤ 160 mg/dL or ≤ 8.9 mmol/L within 21 days and under appropriate anti-diabetic treatment, resume capivasertib at 1 lower dose level. • If fasting blood glucose does not decrease to ≤ 160 mg/dL or ≤ 8.9 mmol/L within 21 days following appropriate antidiabetic treatment, permanently discontinue capivasertib
Grade 4 Life-threatening consequences; urgent intervention indicated	Appropriate clinical management of hyperglycemia per local guidelines. • Consider consult with the diabetologist. • Consider permanent cessation of capivasertib
** Participants may receive education on lifestyle changes (eg, a diabetic diet) and consider beginning home glucose monitoring (eg, fasting self-blood glucose monitoring [SBGM] once-daily) at the discretion of the investigator. If glucose home monitoring is instituted, the capivasertib treatment decision should be based on the morning fasting glucose value obtained prior to the dose of capivasertib*	

6.3.4.3 *Use of metformin*

Metformin is currently the preferred oral antidiabetic recommended for the management of hyperglycaemia occurring in patients participating in studies of capivasertib. Investigators should exercise caution in the dosing and management of patients receiving the metformin/capivasertib combination and must be vigilant for signs of renal impairment and metformin toxicity, such as lactic acidosis and hypoglycaemia, namely: lethargy, hypotension, poor urine output, drowsiness, irritation, tachypnoea, sweating, diarrhoea, and vomiting.

Due to the potential interaction of metformin and capivasertib (caused by inhibition of renal transporters [e.g., OCT2] involved in the excretion of metformin), when taking both capivasertib

and metformin concurrently, patients have renal function monitored once per cycle and as needed if changes in health status occur (e.g., severe infection).

Metformin should only be given on the days when capivasertib is also administered (the half-life of capivasertib is approximately 7-15 hours), and should be withdrawn when treatment with capivasertib is withdrawn, unless otherwise clinically indicated.

Consider withholding of metformin on the days patients are due to have imaging with contrast (in order to reduce the already low risk of lactic acidosis) as per local guidelines.

6.3.4.4 *Maculo-papular rash*

Dose modifications for capivasertib-related maculo-papular rash, which is the most frequent skin toxicity observed in patients treated with capivasertib, are provided in **Table 13**. However, these management guidelines can be used for other skin toxicities at the discretion of the investigator and/or following consultation with the dermatologist.

Table 13. Dose modifications for capivasertib-related maculo-papular rash

NCI CTCAE v5 Toxicity Grade	Management
Grade 1 or 2	Continue dosing at current dose and initiate dermatological treatment: • Topical steroid of moderate strength (twice daily) • Non-sedating oral antihistamines
Grade ≥3	Withhold dosing for up to 28 days and initiate dermatological treatment (topical steroid of moderate strength and non-sedating oral antihistamines) with oral steroid for a short course (e.g., up to 2 weeks). Consultation with dermatologist is advised
• Improves to Grade ≤ 1 and tolerable within 28 days from onset	• Continue dermatological treatment* and restart dosing at same dose
• Improves to Grade 2 and tolerable within 28 days from onset	• Continue dermatological treatment* and restart dosing at reduced dose (1 dose level; **Table 10**)
• Does not improve to Grade 2 and tolerable within 28 days from onset	• Continue dermatological treatment* and discontinue drug
Recurrence of Grade ≥3 or Grade 4 (e.g., severe bullous, blistering or exfoliating skin conditions), or any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Discontinue capivasertib
** In participants with persistent rash or previous occurrence of grade 3 consider secondary prophylaxis by continuing topical steroids and/or non-sedating oral antihistamines*	

6.3.4.5 *Hypersensitivity*

In the case of hypersensitivity reactions, capivasertib should be discontinued and symptomatic/supportive therapy should be initiated (including with antihistamines and/or steroids) as considered appropriate by the investigator/treating physician. Drug rechallenge is not recommended; any subsequent consideration on rechallenge with capivasertib at the same or a lower dose, with its potential for recurrence of such or more severe events should be carefully considered against the potential benefits to the individual patient from continuation of capivasertib therapy. Further management should follow local guidelines on management of hypersensitivity reactions.

6.3.4.6 *Diarrhea*

Participants should be instructed to promptly contact investigators if they develop diarrhea. **Alternative etiologies should be ruled out prior to initiating the dose modifications.** Investigators are recommended to prescribe anti-diarrheal treatment at the first visit so that participants can start treatment at the first sign of diarrhea, should it occur. Loperamide is the preferred anti-diarrhea agent for the management of diarrhea occurring in patients participating in studies of capivasertib.

If diarrhea is reported, additional details regarding this AE should be collected in the appropriate eCRF. Guidelines for dose modifications for capivasertib-related diarrhea are shown in **Table 14**.

Table 14. Dose modifications for capivasertib-related diarrhea

NCI CTCAE v5 Toxicity Grade	Management
Grade 1	Maintain same capivasertib dose. Anti-diarrheal treatment (e.g., loperamide) should be initiated at first report of diarrhoea. Maximize the supportive care (e.g. dietary modifications, appropriate hydration therapy and electrolyte supplements as clinically indicated).
Grade 2	Interrupt capivasertib dose (up to 21 days) until recovery to ≤ Grade 1 and resume dosing at same dose level. Anti-diarrheal treatment (eg loperamide) should be initiated at first report of diarrhoea. Maximize the supportive care (e.g. dietary modifications, appropriate hydration therapy and electrolyte supplements as clinically indicated) Consider secondary prophylaxis*
Grade ≥3	Interrupt capivasertib dose (up to 21 days) and institute appropriate anti-diarrheal treatment
• Improves to Grade ≤1 within 21 days	Resume dosing at same dose or one reduced dose level (**Table 10**) as clinically appropriate maintaining treatment for toxicity as necessary and/or start secondary phophylaxis*
• Does not improve to Grade ≤1 after 21 days or remains clinically intolerable	Discontinue drug

Table 14. Dose modifications for capivasertib-related diarrhea	
NCI CTCAE v5 Toxicity Grade	**Management**
Recurrence of Grade ≥2 or clinically significant or intolerable toxicity despite secondary prophylaxis	Interrupt capivasertib dose (up to 21 days), maintaining appropriate anti-diarrhoeal treatment
Improves to Grade ≤1 or becomes clinically tolerable within 21 days	Resume dosing up to two reduced dose levels as clinically appropriate maintaining treatment for toxicity as necessary and/or maintaining secondary phophylaxis*
Does not improve to Grade ≤1 clinically significant or remains clinically intolerable after 21 days	Discontinue capivasertib
*In participants with persistent Grade 1 diarrhea (e.g., loperamide 2 mg, 2 to 4 times daily).	

6.3.5 MANAGEMENT OF SELUMETINIB-RELATED TOXICITIES

Any selumetinib-related toxicity observed during the course of the study can be managed by interuption of the dose of study treatment or dose reductions according to the dose reductions provided in **Table 15** and **Table 16**, and the toxicity management guidelines provided in Sections 6.3.5.1 to 6.3.5.8. Unless otherwise stated, two dose reductions are allowable after which study treatment should be discontinued.

Table 15. Selumetinib recommended dosage based on body surface area	
Body Surface Area (BSA)	**Recommended Dosage**
0.55 – 0.69 m^2	20 mg in the morning and 10 mg in the evening
0.7 – 0.89 m^2	20 mg twice daily
0.90 – 1.09 m^2	25 mg twice daily
1.10 – 1.29 m^2	30 mg twice daily
1.30 – 1.49 m^2	35 mg twice daily
1.50 – 1.69 m^2	40 mg twice daily
1.70 – 1.89 m^2	45 mg twice daily
≥1.90 m^2	50 mg twice daily
a. The recommended dosage for participants with a BSA <0.55 m^2 has not been established	

Treatment with selumetinib should be temporarily interrupted if one of the following AEs occurs and is considered related to treatment with selumetinib:

- Any intolerable AE regardless of grade.
- Any AE CTCAE grade 3.

On improvement of the AE to CTCAE grade 1 or less within 4 weeks of onset, study treatment may be restarted at the discretion of the investigator. If restarted, it must be at a reduced dose as shown in **Table 16**. If the AE does not resolve to CTCAE Grade 1 or less within 4 weeks of onset, study intervention must be permanently terminated unless otherwise specified.

The dose modification procedure is shown in **Table 16**. Two step dose modification is applied

in the study. Any participants with 2 prior dose reductions who experience a toxicity that would cause a third dose reduction must be discontinued from study intervention. Dose must not be re-escalated following dose reduction apart from to account for increase due to BSA, in accordance with **Table 16**. For example, if a participant has a BSA of 1.8 m^2 and starts on a dose of 45 mg BID and then has a dose reduction to 35 mg AM, 30 mg PM then a subsequent BSA increase to 1.9 m^2 would mean the participant should be dose adjusted to 35 mg BID.

Note that if selumetinib treatment is interrupted for > 4 weeks for any reason other than AEs related to selumetinib eg, investigations, unplanned procedures and AEs unrelated to selumetinib, re-start of treatment must be discussed with the Investigator.

Treatment with selumetinib should be permanently discontinued for any CTCAE Grade 4 toxicity that is at least partially related to selumetinib. However, if it is felt to be in the best interest of the participant, interruption of selumetinib with potential to restart at a reduced dose upon resolution to Grade 1 or less may be considered on a case-by-case basis for CTCAE Grade 4 AEs in consultation with the Principal Investigator.

Table 16. Selumetinib recommended dose reduction for adverse reactions

BSA	Initial Selumetinib Dose[a] (mg/twice daily)	First dose reduction (mg/dose)		Second dose reduction (mg/dose)[b]	
		Morning (AM)	Evening (PM)	Morning (AM)	Evening (AM)
0.55 – 0.69 m^2	20 mg in the morning and 10 mg in the evening	10	10	10 once daily	
0.7 – 0.89 m^2	20	20	10	10	10
0.90 – 1.09 m^2	25	25	10	10	10
1.10 – 1.29 m^2	30	25	20	20	10
1.30 – 1.49 m^2	35	25	25	25	10
1.50 – 1.69 m^2	40	30	30	25	20
1.70 – 1.89 m^2	45	35	30	25	20
≥1.90 m^2	50	35	35	25	25

a. Based on BSA as shown in **Table 15**
b. Permanently discontinue selumetinib in participants unable to tolerate selumetinib after two (2) dose reductions.

6.3.5.1 *Diarrhea*

Participants should be instructed to promptly contact investigators if they develop diarrhea. Investigators are recommended to prescribe anti-diarrheal treatment at the first visit so that participants can start treatment at the first sign of diarrhea, should it occur. Alternative etiologies should be ruled out prior to initiating the dose modifications. If diarrhea is reported, additional details regarding this AE should be collected in the appropriate eCRF. Guidelines for dose modifications for selumetinib-related diarrhea are shown in **Table 17**.

Table 17. Selumetinib Recommended Management for Diarrhea
Grade 1 or 2 uncomplicated diarrhea
Continue selumetinib treatment and monitor as clinical indicated. Treat with loperamide in accordance to local practice. Dietary management* (1) If diarrhea resolving or resolved after 12 hours of loperamide, then: • Continue loperamide for 12 hours after diarrhoea resolved • Adjust diet
(2) If persistent diarrhea not resolved after 12 hours of loperamide and remains uncomplicated CTC Grade 1 or 2: • Consider increasing loperamide to maximum dose & frequency in accordance to local labels. • Consider additional agents according to local practice if loperamide is not adequate to control diarrhea as a single agent o If diarrhea resolves or resolved after 24 hours, then continue loperamide for 12 hours after diarrhoea resolved and adjust diet o If persistent diarrhea not resolved after 24 hours, then ▪ Interrupt selumetinib dose, ▪ Conduct full examination, ▪ Treat according to local practice (e.g., rehydration, electrolytes, antibiotics, hospitalization)
Grade 1 or 2 Complicated Diarrhea or Grade 3 or 4 Diarrhea at any time**
• Interrupt selumetinib dose, • Hospitalization. • Treat according to local practice (eg. rehydration, electrolytes, antibiotics).
*BRAT diet (bananas, rice, apple sauce, toast, plain pasta), readily digestible food, avoidance of lactose-containing products and fried, fatty or spicy foods, increased fluid intake (8-10 glasses of clear fluids/day (including water, clear broth, fluids containing salt and sugar). **Diarrhea complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension

6.3.5.2 *Visual Disturbances*

Participants experiencing visual disturbances should undergo a complete ophthalmologic examination (to evaluate for selumetinib-related toxicity such as retinal layer separation/edema), as described in Section 7.1.9. Consider interruption of selumetinib at investigator discretion whilst awaiting ophthalmologic assessment. Refer to **Table 18** for further management guidelines.

Table 18. Selumetinib Management of Retinal Pigment Epithelial Detachment (RPED), Central Serous Retinopathy (CSR), or Retinal Vein Occlusion (RVO)
No diagnosis of RPED/CSR/RVO: • **Continue selumetinib** • Manage visual symptoms according to local practice

Table 18. Selumetinib Management of Retinal Pigment Epithelial Detachment (RPED), Central Serous Retinopathy (CSR), or Retinal Vein Occlusion (RVO)
Diagnosis of RPED / CSR: (1) If best corrected visual acuity 20/40 or better, or not worsened from baseline if there is pre-existing visual impairment, then: • **Continue selumetinib** • Repeat ophthalmic assessments every 3 weeks until resolution
(2) If best corrected visual acuity worse than 20/40, or worsened from baseline if there is pre-existing visual impairment, then: • **Interrupt selumetinib** • On resolution to 20/40 or better, or baseline if there is pre-existing visual impairment, within 3 weeks, selumetinib may be restarted after a dose reduction
Diagnosis of retinal vein occlusion (RVO) • **Discontinue selumetinib**

6.3.5.3 *Rash*

Treatment of rash should be managed in accordance with institutional standards. **Table 19** provides additional management guidelines. To reduce rashes, prophylactic recommendations are to start on day 1 of treatment with selumetinib and continue for the whole duration of treatment. This may include applying a skin moisturiser (thick, alcohol-free) at bedtime, avoiding excessive exposure to sunlight, and avoiding the use of topical retinoids or benzoyl peroxide, as these are not recommended.

Table 19. Selumetinib Management of Rash		
Toxicity	**Dose Guidelines**	**Recommended Management**
Grade 1 or 2 **Tolerable Rash**	• Continue Selumetinib treatment and monitor as clinical indicated. • Manage rash as per paediatric or adult treatment recommendations.	Grade 1 rash: • Apply a mild/moderate strength • topical steroid • and/or topical antibiotic. Grade 2 rash (tolerable): • Apply a moderate strength topical steroid and consider an oral antibiotic
Grade 2 Intolerable, or **Grade ≥3**	• Consider Selumetinib dose interruption. • Consider referral to a dermatologist. • Manage rash as per paediatric or adult treatment recommendations. *If rash has improved to Grade 2 tolerable or less within 4 weeks, restart selumetinib at original dose*	Grade ≥3 rash or Grade 2 rash considered by the participant to be intolerable: • Apply moderate strength topical steroid and consider an oral antibiotic. If an infection is suspected, consider other broad spectrum antibiotic cover.

	or consider reduced dose.	

6.3.5.4 *Paronychia*

Treatment of rash should be managed in accordance with institutional standards. **Table 20** provides additional management guidelines.

Table 20. Selumetinib Management of Paronychia

Toxicity	Dose Guidelines	Recommended Management
CTC Grade 1 or 2 Tolerable	Continue selumetinib treatment and monitor as clinical indicated. Manage per treatment recommendations.	Grade 1: Treat the affected area by soaking in vinegar solution twice daily (1 part vinegar to 2 parts water), plus topical antibiotic mupirocin (or similar agent) twice daily.
Grade 2 Intolerable or Grade ≥3	• Consider selumetinib dose interruption. • Consider referral to a dermatologist. • Manage paronychia as per treatment recommendations. *If paronychia has improved to Grade 2 tolerable or less within 4 weeks, then re-start selumetinib at original dose or consider reduced dose.*	Grade 2: Treat the affected area by soaking in vinegar solution twice daily (1 part vinegar to 2 parts water), plus systemic antibiotic (e.g., keflex, clindamycin), as well as high potency steroid (e.g., 0.05% clobetasol ointment covered with saran wrap or flurandrenolide tape (e.g., cordran tape) applied at bedtime. This should be removed in the morning. Grade 3: If severe, seek consult for incision & drainage or surgical management. *If granulation tissue present, consider use of silver nitrate under supervision

For participants who do not undergo drainage, silver nitrate may be used, as well as topical bactroban, steroids, and/or antifungals. Silver nitrate is only of value when there is open inflamed skin or granulation tissue (e.g. pyogenic-granuloma-like lesions). If the periungual skin is swollen but intact (whether infectious or non-infectious), silver nitrate is not recommended. Participants should be cautioned to avoid trauma to the area. Podiatry consult may be considered for partial nail removal.

Participants who undergo incision and drainage and are found to have no infectious organisms on culture, should be treated as above. If infection is identified, participants may be treated with systemic antibiotics (oral tetracyclines). If paronychia recurs or develops in other fingers or toes, Flurandrenolide (e.g. Cordran) tape or topical steroid cream such as triamcinolone can be used in the morning and Bactroban and Nizoral topical ointments in the evening.

6.3.5.5 *Oral Mucositis*

Oral care guidelines for events of oral mucositis and dry mouth:

- Participants should be encouraged to follow a daily oral health care regimes, both before and during treatment with selumetinib.
- Participants with a healthy mouth may use non alcoholic mouthwash 4 to 6 times daily (e.g. after each meal), or according to the instructions, during the study.
- Saline mouthwashes (Sodium chloride 0.9%) are preferred to alcohol-based mouth washes in cases of stomatitis, and should be used at a different time than toothbrushing (e.g. after tea).
- Use of a mouthwash immediately after selumetinib intake is recommended.
- The tongue can be gently brushed (if not sore) with a soft toothbrush.
- Participants with, or at risk of, stomatitis should not use commercial/over-the-counter mouthwashes because of the alcohol content and astringency. Chlorhexidine mouthwashes are not recommended for the treatment of established stomatitis.
- The mouth should be regularly inspected by the participants and healthcare professionals.
- Teeth should be brushed twice daily with a fluoride toothpaste and soft toothbrush, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating. The toothbrush should be replaced regularly (at least every 3 months).
- Participants with stomatitis should change their toothbrush every 4 - 6 weeks.
- Investigators or treating physician should consider culture to rule out herpes simplex.
- Investigators or treating physician should consider treating stomatitis at an early stage (i.e., CTCAE grade 1) or as soon as the participant complains of a sore mouth. Consider using an oral topical analgesic, with or without topical steroids, depending on the patient's clinical condition and institutional standards.

6.3.5.6 *Creatine Kinase (CK) Elevation*

Elevated CK should be managed in accordance with institutional standards. **Table 21** provides additional management guidelines.

Table 21. Selumetinib Management of Elevated Creatine Kinase

Toxicity	Management
Grade 1 or 2, **CK > ULN to ≤ 5x ULN**	Continue selumetinib and CK monitoring as per protocol or more frequently if onset of new or worsening muscle symptoms or as per Investigator's clinical judgment

Grade 3,
CK > 5x to ≤10x ULN
	• Consider selumetinib interruption
	• Evaluate patient for new or worsening of existing muscle symptoms
	(1) If no muscle symptoms, then:
	  • Continue selumetinib and CK monitoring as per protocol or more frequently if onset of new or worsening muscle symptoms or as per Investigator's clinical judgment
	(2) If new or worsening muscle symptoms, then:
	  • Interrupt selumetinib
	  o Measure serum creatinine and urine myoglobin levels
	  o Consider muscle biopsy or electromyography
	  • If no evidence of rhabdomyolysis, then:
	  o If CK levels have improved to grade 1 or less and symptoms resolve to baseline within 3 weeks, selumetinib may be restarted at reduced dose

Table 21. Selumetinib Management of Elevated Creatine Kinase	
Toxicity	**Management**
	• If evidence of rhabdomyolysis, then: o Discontinue selumetinib o Manage according to local institutional standards
Grade 4 **CK > 10 x ULN**	• Interrupt selumetinib o Measure serum creatinine and urine myoglobin levels o Consider muscle biopsy or electromyography • If no evidence of rhabdomyolysis, then: o If CK levels have improved to grade 1 or less and symptoms resolve to baseline within 3 weeks, selumetinib may be restarted at reduced dose • If evidence of rhabdomyolysis, then: o Discontinue selumetinib o Manage according to local institutional standards

6.3.5.7 *Dyspnea*

The following should be considered for investigation of new or worsening of pre-existing dyspnea, and may include: based on clinical examination: chest X-ray: P-A and lateral view, echocardiography, ECG; WBC, Hb, BNP, troponin, sputum culture, renal panel, blood or urine culture. Consider at the investigator discretion, interruption of selumetinib whilst investigations are ongoing. **Table 22** provides guidelines for the investigation and management of dyspnea that may be related to selumetinib.

Table 22. Selumetinib Management of Dyspnea
If diagnosis other than pneumonitis/ILD, then: • Manage according to local institutional standards (1) If dypnea resolves to baseline, then continue selumetinib: (2) If treatment is ineffective, then: • Perform high resolution CT scan. • Consider respiratory consultation. • If no diagnosis of pneumonitis/ILD by high resolution CT, and dyspnea not resolved to baseline, then: o Cardiology / respiratory consultation.
If suspected pneumonitis/ILD or no obvious cause of dyspnea, then: • Perform high resolution CT scan. • Consider respiratory consultation. (1) If no diagnosis of pneumonitis/ILD by high resolution CT, and dyspnea not resolved to baseline, then: • Cardiology / respiratory consultation. (2) If diagnosis of pneumonitis/ILD by high resolution CT, then: • Treat according to local practice. Selumetinib will be held for grade ≥2 pneumonitis for up to 3 weeks. • If event resolves to Grade ≤1 after withholding for up to 3 weeks then selumetinib may be restarted. Consider reduced dose. • If event does not resolve to Grade ≤1 by 3 weeks then discontinue selumetinib.

6.3.5.8 *Left Ventricular Ejection Fraction (LVEF) Reduction or Dysfunction*

Refer to **Table 23** for selumetinib management of LVEF reduction or dysfunction.

Table 23. Selumetinib Management of LVEF

Toxicity	Management
LVEF ≥ LLN	If LVEF has decreased from baseline ≥10 percentage points, then: • Continue selumetinib. • ECHO after 3-6 weeks.
LVEF < LLN, but >39%	(1) If LVEF has decreased from baseline <10 percentage points, then: • **Continue selumetinib.** • Cardiology consult • ECHO after 3-6 weeks. (2) If LVEF has decreased from baseline ≥10 percentage points but <20 percentage points, then: • **Hold selumetinib.** • Cardiology consult. • ECHO after 3-6 weeks. • If LVEF recovers to ≥ LLN within a period of 3 months or less, selumetinib may be restarted at a reduced dose based on cardiology recommendation. (3) If LVEF has decreased from baseline ≥20 percentage points, then: • **Discontinue selumetinib.** • Manage according to local practice. • Refer to a cardiologist.
LVEF < 39%, or Grade ≥3 Left Ventricular Systolic Dysfunction	• **Discontinue selumetinib.** • Manage according to local practice. • Refer to a cardiologist.

6.3.6 MANAGEMENT OF CERALASERTIB-RELATED TOXICITIES

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 3-4 weeks on each occasion (depending on the toxicity and treatment arm). If study treatment cannot be restarted within the specified period, then the participant must permanently discontinue study treatment.

If a participant experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted, and supportive therapy administered as required. If the toxicity resolves or reverts to ≤ CTCAEv5 grade 1 or 2 (depending on the toxicity, seeTable 24) treatment with ceralasertib may be restarted using the rules in **Table 24 and Table 25** for dose modifications. Participants 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 ≤ CTCAEv5 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 4. If the duration of ceralasertib dose interruption is longer than 28 days, the case should be discussed with the Study Physician.

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 Study Physician.

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

The dose of study treatment must not be adjusted under any other circumstances unless prior agreement is given by the study physician.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions must be recorded.

6.3.6.1 *Dose reductions for Ceralasertib monotherapy*

Refer to **Table 24 and Table 25** for dose modification and stopping criteria for ceralasertib.

Please note that for simultaneous toxicities (for example, anaemia 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, anaemia 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 24. Guidance for dose modifications and interruptions for ceralasertib

Event	Action
Grade 1 neutropenia and/or thrombocytopenia	Ceralasertib dosing may continue if neutrophil count is ≥1500/mm^3 and/or platelet count is ≥75,000/mm^3.
Grade 1-2 toxicities (except neutropenia and thrombocytopenia)	Investigator decision whether to interrupt ceralasertib (max 28 days) or continue treatment. Treatment may be resumed at the same dose level or with a dose reduction by 1 level.
Grade 2 neutropenia or grade 3 anaemia	Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment e.g. transfusion, until AE improves to at least neutrophil count ≥1500/mm^3 and haemoglobin ≥8.0 g/dL, then

	restart reducing the dose of ceralasertib by 1 level[a]. If a further dose reduction is required after the level 3 dose reduction, the patient must stop treatment.
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment until platelets improve to at least ≥100,000/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 (max 28 days) and give appropriate supportive treatment. Treatment may be restarted with a reduced dose of ceralasertib when the toxicity is resolved or investigator discretion to stop treatment.
Grade 4 thrombocytopenia	Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment; investigator discretion on whether to restart treatment with a dose reduction by 1 dose level ceralasertib when the platelet count has recovered to ≥100,000/mm^3 or stop treatment.
Grade 3-4 toxicity (except grade 3 anaemia and grade 3-4 thrombocytopenia)	**First occurrence** Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment; restart treatment with a dose reduction by 1 level for ceralasertib when the toxicity is resolved (grade 1 or 2 depending on the toxicity or returns to baseline). **Subsequent occurrences** Investigator discretion on whether to interrupt ceralasertib (max 28 days) or to stop treatment. Restart treatment reduced by 1 or 2 levels dose of ceralasertib. If a further dose reduction is required after the level 3 dose reduction, the patient must stop treatment.

Vomiting	If vomiting occurs shortly after ceralasertib is swallowed, the dose should only be replaced if all of the intact tablets 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.

[a] This table is for guidance. Therefore, for example, it may be deemed appropriate by the investigator to reduce the dose by more than one dose level depending on the individual patient circumstances.

Table 25. Dose reduction levels for ceralasertib

Initial dose	**240 mg BID days 1–14**
Level 1 dose reduction	160 mg BID days 1–14
Level 2 dose reduction	120 mg BID days 1–14
Level 3 dose reduction	80 mg BID days 1–14
Level 4 dose reduction	Stop treatment

6.3.6.2 *Individual stopping criteria*

6.3.6.2.1. 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 G.

6.3.6.2.2. 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.

6.3.6.3 *Ceralasertib as CYP3A drug substrate*

The principal enzyme for metabolizing ceralasertib is CYP3A4. 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 (five half-lives) before dosing ceralasertib again. If potent CYP3A inducers are considered necessary for the participant's safety and welfare, this may diminish the clinical efficacy of ceralasertib, and the participant should be monitored carefully for any change in the

efficacy of the study treatment. Refer to Section 6.6.5 for additional information.

6.3.6.4 *Ceralasertib as Pgp drug substrate*

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 participant'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 Section 6.6.5 for additional information.

6.3.6.5 *Ceralasertib as Pgp drug substrate*

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 BRCP modulator (five half-lives) before dosing ceralasertib again. Refer to Section 6.6.5 for additional information.

6.4 TREATMENT PERIOD AND MAINTENANCE

A treatment cycle is defined as the first day of study drug administration (Day 1) through and including Day 28. All eligible participants will receive cycle 1 induction treatment with 4 weeks of olaparib (28 days ± 7 days), as described in Section 6.1.1. After completing the 4-week Cycle 1 olaparib monotherapy, eligible participants will proceed to receive olaparib in combination with either durvalumab, selumetinib, or capivasertib, or ceralasertib monotherapy, based on treatment arm assignment for 12 cycles (i.e., approximately 48 weeks). Following the completion of all 13 on-study treatment cycles (for all study arms), participants will be considered off-treatment. Participants deriving clinical benefit from treatment may, at the investigator's discretion and in the absence of disease progression or unacceptable toxicity, continue on assigned therapy beyond the planned 13 cycles. Clinical data regarding survival outcomes for all participants will continue to be collected for the duration of the trial (i.e., up to 12 months post-treatment).

6.5 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Medications required to treat AEs, manage cancer symptoms, concurrent diseases, and supportive care agents, such as pain medications, anti-emetics, and antidiarrheals are allowed in general. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment. All medications (other than investigational products) and significant non-drug therapies (including vitamins, herbal medications, physical therapy, and blood transfusions) administered during the study must be listed on the appropriate eCRF.

6.5.1 PNEUMONITIS

Grade 2 events may be treated with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Participants with Grade 3-4 events should be immediately treated with intravenous steroids. Additional anti-inflammatory measures may be administered as needed. Prophylactic antibiotics

for opportunistic infections in the case of prolonged steroid administration may also be given. If the participant is determined to have study drug-associated pneumonitis, the suggested treatment plan is detailed in the separately provided durvalumab TMG.

6.5.2 DIARRHEA/COLITIS

From screening onwards, should a participant develop diarrhea, then these symptoms should be reported as AEs (see Section 9.2) and appropriate treatment of the event given.

Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and bowel perforation (such as peritoneal signs and ileus). In symptomatic participants, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

For Durvalumab: In participants with severe enterocolitis, durvalumab will be permanently discontinued, and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In participants with moderate enterocolitis, durvalumab should be withheld, and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 1 to 2 mg/kg/day of prednisone or equivalent).

All participants that experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

6.5.3 NAUSEA/VOMITING

From screening onwards, should a participant develop nausea or vomiting, then these symptoms should be reported as AEs (see Section 9) and appropriate treatment of the event given.

For Olaparib: No routine prophylactic anti-emetic treatment is required at the start of treatment; however, the participant should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter per institutional guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack.

For Durvalumab: nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.

6.5.4 ANEMIA

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia but should be clearly noted as concurrent medications

For Olaparib or Ceralasertib: Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed per

institutional guidelines. In some cases, the management of anemia may require blood transfusions. For cases where participants develop prolonged hematological toxicity (≥2 week interruption/delay in program treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Sections 6.3.1.3 (olaparib) and 6.3.6 (ceralasertib) for the management of prolonged hematological toxicity.

6.5.5 THROMBOCYTOPENIA

Transfusion of platelets may be used if clinically indicated. Idiopathic thrombocytopenic purpura should be ruled out before initiation of platelet transfusion.

6.5.6 DIABETES MELLITUS

Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

For Capivasertib: hyperglycemia should be managed as described in Section 6.3.4.2.

6.5.7 HYPOPHYSITIS / ADRENAL INSUFFICIENCY

Participants showing Grade 2 symptoms may be treated with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. Participants with Grade 3-4 events should be treated with an initial dose of IV corticosteroids, followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.5.8 HYPERTHYROIDISM OR HYPOTHYROIDISM

Thyroid disorders can occur at any time during treatment. Participants should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Participants with grade 2 hyperthyroidism events may receive non-selective beta-blockers (e.g., propranolol) as a suggested initial therapy. Participants with grade 2 hypothyroidism, may receive thyroid hormone replacement therapy, with levothyroxine or liothyronine, per institutional guidelines.

Participants with Grade 3-4 hyperthyroidism may be treated with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.5.9 HYPERPHOSPHATEMIA

Management of hyperphosphatemia, including diet modifications, phosphate binders, and diuretics, should be in accordance with institutional guidelines.

6.5.10 HEPATIC ADVERSE EVENTS

Participants with Grade 2 events should be treated with IV or oral corticosteroids per institutional guidelines. Participants should undergo more frequent monitoring (i.e., weekly) of liver function until values return to baseline.

Participants with Grade 3-4 events should be treated with IV corticosteroids for 24 to 48 hrs. Once symptoms resolve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.5.11 NEPHRITIS AND RENAL FAILURE

Participants with Grade 2 events may be treated with corticosteroids. For those with Grade 3-4 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.5.12 INFECTION PROPHYLAXIS

Participants with documented infectious complications should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the Investigator for a given infectious condition, according to standard institutional practice.

6.5.13 IMMUNE-RELATED AND/OR HYPERSENSITIVITY REACTIONS

In the event of suspected immune-related adverse events (irAEs) or hypersensitivity, the durvalumab infusion or other study agents (e.g., selumetinib) should be immediately discontinued, and appropriate supportive therapy should be administered per institutional guidelines, which may include (but not limited to): epinephrine, IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines, or acetaminophen.

Participants with Grade 2 symptoms may be premedicated with Diphenhydramine, 50 mg PO (or equivalent dose of antihistamine), as well as acetaminophen, 500-1000 mg PO (or equivalent dose of antipyretic).

Durvalumab should be withheld in participants with Grade 3 and Grade 4 irAEs. Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. Prednisone or equivalent may be utilized at 1 to 2 mg/kg per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. Durvalumab should be discontinued if unable to reduce corticosteroid dose to <10 mg per day prednisone or equivalent within 12 weeks of toxicity.

Refer to Section 6.3.4.5 regarding the management of capivasertib-related hypersensitivity.

6.5.14 DIET

Participants should maintain a normal diet unless modifications are required to manage an AE, such as diarrhea, nausea, or vomiting.

6.5.15 BLOOD DONATION

Participants should not donate blood while participating in this study, or for at least 90 days after receipt of the final dose of durvalumab, or until after 4-5 times the half-life of durvalumab or until the time specified in the prescribing information of durvalumab, whichever occurs longest.

Participants assigned to receive selumetinib should avoid donating blood for at least 12 weeks after receiving the last dose of the study medications or for longer if required in accordance with the prescribing information for the concomitantly administered olaparib.

6.5.16 DERMATOLOGICAL CARE

Rashes (acneiform [papulopustular]) should be managed according to institutional standards. Early initiation of treatment is recommended for dermatological events that are known to occur with study agents (e.g., selumetinib). Dry skin is commonly reported during treatment with selumetinib monotherapy (typically CTCAE Grade 1), and the use of alcohol-free moisturizer at bedtime is recommended during treatment with this study drug.

Phototoxicity is not designated an important risk, but as ceralasertib is an inhibitor of DNA damage repair, and participants are advised to take precautions when outside in the sun, e.g., limiting the duration of sun exposure, wearing protective clothing (hat and sunglasses) and sunscreen.

6.5.17 VISUAL FUNCTION

Blurred vision, generally CTCAE Grade 1, has been reported in some patients enrolled in studies of selumetinib monotherapy or in combination with other anti-cancer agents. AEs consistent with CSR/RPED and with retinal vein occlusion have also been reported in a small number of patients receiving treatment with selumetinib. Ophthalmologic exams in participants with reported visual AEs or change in visual acuity should be performed according to institutional standards. Consultation with an ophthalmologist is recommended as clinically appropriate.

6.5.18 CONTRACEPTION

Study agents described within this protocol may have adverse effects on a fetus in utero. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use appropriate methods of birth control described in Appendix D) or are considered highly unlikely to conceive.

Highly unlikely to conceive women are defined as:

1. Surgically sterilized, or
2. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    a. Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    b. Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

3. Not heterosexually active for the duration of the study.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 9.7. If there is any question that a participant will not reliably comply with the requirements for contraception, they should not be entered into the study.

6.5.19 USE IN PREGNANCY

If a participant inadvertently becomes pregnant while on treatment with olaparib and/or durvalumab, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The pregnancy will be recorded on the eCRF and reported by the Investigator to the IRB (refer to Section 9.7.3) and any other entity, as required per protocol

6.5.20 USE IN NURSING WOMEN

It is unknown whether any of the study agents is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

6.6 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Prohibited medications associated with olaparib are shown in **Table 26**. Restricted concomitant medications associated with olaparib are shown in **Table 27**.

6.6.1 OLAPARIB

Table 26. Prohibited medications - Olaparib -	
Prohibited medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed)**
Anticancer therapy: Chemotherapy Immunotherapy Monoclonal Antibodies against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study Hormonal therapy* Radiotherapy (except palliative) Biological therapy Other novel agents	Not permitted while the participant is receiving study medication
CYP2C19	***lansoprazole, omeprazole, S-mephenytoin***
P-gp	***simvastatin, pravastatin, digoxin, dabigatran, colchicine***
Live virus vaccines **Live bacterial vaccines**	Not permitted while the participant 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.
OCT2 -	***Serum creatinine***
OAT3 -	***Furosemide, methotrexate***
*Hormone Replacement Therapy (HRT) is acceptable	

Table 27. Restricted concomitant medications - Olaparib	
Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should not be taken with *olaparib*. If there is no suitable alternative concomitant medication then the dose of *olaparib* should be reduced for the period of concomitant administration. The dose reduction of *olaparib* should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of *Olaparib* to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors - reduce the dose of *olaparib* to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. After the washout of the inhibitor is complete, the *olaparib* dose can be re-escalated.

Table 27. Restricted concomitant medications - Olaparib

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Strong inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with o*laparib.* If the use of any strong or moderate CYP3A inducers are considered necessary for the participant's safety and welfare this could diminish the clinical efficacy of olaparib. If a participant requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of *olaparib*
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Participants who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a participant undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Table 27. Restricted concomitant medications - Olaparib	
Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Administration of other anti-cancer agents	Participants must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Participants 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.

6.6.2 DURVALUMAB

Prohibited medications associated with durvalumab are shown in **Table 28**.

Table 28. Prohibited Concomitant Medications - Durvalumab	
Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the participant is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the participant is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the participant is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])

Table 28. Prohibited Concomitant Medications - Durvalumab	
Prohibited medication/class of drug:	**Usage:**
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding <<10 mg/day>> of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Use in participants with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the participant (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
EGFR TKIs <<unless the study is assessing the combination of an EGFR TKI and durvalumab>>	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the investigator

6.6.3 CAPIVASERTIB

6.6.3.1 *Drugs that may influence capivasertib pharmacokinetics*

Based on results from in vitro studies, capivasertib is primarily metabolised by CYP3A4 and UGT2B7 enzymes. Therefore, inhibitors or inducers of these enzymes may increase or decrease exposure, respectively, to capivasertib. The potent inducer enzalutamide reduced the systemic exposure to capivasertib by approximately 50%. There are no other confirmed clinical drug interactions with capivasertib. The potential interactions are considered on the basis of non-clinical data and physiology-based PK modelling.

Strong inhibitors and strong inducers of CYP3A4 must not be combined with capivasertib and must be stopped at least 2 weeks before the first dose of capivasertib (3 weeks for St John's Wort and 4 weeks for enzalutamide). Strong inhibitors must not be used for 2 days following discontinuation of capivasertib. Moderate inhibitors and inducers of CYP3A4 or UGT2B7 inhibitors and inducers are permitted, but caution should be exercised and participants monitored closely for possible drug interactions. Drugs known to be inhibitors and inducers of CYP3A4 or UGT2B7 are presented in **Table 29** and **Table 30** are not intended to be exhaustive

and a similar restriction will apply to other agents that are known to modulate CYP3A4 activity. Appropriate medical judgment is required. Investigators are directed to contact sponsor-PI with any queries you have on this issue.

Table 29. Drugs known to be inhibitors of CYP3A4 or UGT2B7

Must be stopped 2 weeks prior to capivasertib administration. Must not be used concomitantly with capivasertib and for 2 days following discontinuation of capivasertib:	**Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions:**
Strong CYP3A4 inhibitors boceprevir clarithromycin (+TdP risk) cobicistat danoprevir and ritonavir[a] elvitegravir and ritonavir[a] indinavir and ritonavir[a] itraconazole ketoconazole lopinavir and ritonavir[a] nefazodone nelfinavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[a] posaconazole ritonavir[a] telaprevir telithromycin tipranavir and ritonavir[a] troleandomycin voriconazole	**Moderate CYP3A4 inhibitors** **aprepitant** ciprofloxacin (+TdP risk) cyclosporine diltiazem erythromycin (+TdP risk) fluconazole (+TdP risk) fluvoxamine tofisopam verapamil
Strong or Moderate CYP3A4 inhibitors AND Sensitive CYP3A substrates Follow Guidance in **Table 30**: conivaptan dronedarone saquinavira	**UGT2B7 inhibitors** cannabidiol[b]

a. Ritonavir has dual effects of simultaneous CYP3A inhibition and induction; the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity. Ritonavir is usually given in combination with other protease inhibitors. Please refer to the full Prescribing Information for these drugs prior to co-administration with capivasertib.
b. Cannabidiol is also a CYP3A4 substrate.
c. CYP=Cytochrome P450

TdP risk= Known risk of Torsades de Pointes according to the Arizona Centre for Education and Research on Therapeutics (ArizonaCert) website (https://www.crediblemeds.org/). Consider additional ECG monitoring.

Table 30. Drugs known to be strong or moderate inducers of CYP3A

Must be stopped 2 weeks (3 weeks for St John's Wort)prior to capivasertib administration. Must not be used concomitantly with capivasertib.	**Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions:**

Strong CYP3A inducers	**Moderate CYP3A inducers**
carbamazepine phenytoin rifampicin/rifampin St. John's wort	bosentan efavirenz etravirine phenobarbital primidone

6.6.3.2 *Drugs that may be influenced by capivasertib*

There are currently no clinical data confirming that there are any PK interactions between capivasertib and drugs metabolised by CYP450 enzymes. Likewise, there are no confirmed interactions with renal or hepatic transporter substrates. The potential interactions are considered on the basis of preclinical data and physiology-based PK modelling. These suggest that capivasertib may be a moderate to strong inhibitor of CYP3A4, but a less potent inhibitor of some drug transporters and may thus increase the exposure of some drugs. Capivasertib also inhibited CYP2D6 and CYP2C9 in vitro. However, based on physiology-based PK modelling, the increase in exposure of sensitive substrates for these isoenzymes is not predicted to be clinically relevant (<10%).

The guidance in **Table 31** and **Table 32** are based on the predicted magnitude of increase in exposure and the expected clinical significance of that increase (therapeutic window and/or QT liability). The lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to be sensitive to inhibition of CYP3A or transporter proteins. Please refer to the full Prescribing Information for all drugs prior to co-administration with study intervention and consider dose reduction where clinically applicable.

Table 31. Drugs known to be sensitive or moderate sensitive CYP3A substrates whose exposure, pharmacological action, and toxicity may be increased by capivasertib

Must be stopped 1 week prior to capivasertib administration. Must not be used concomitantly with capivasertib and for 1 week following discontinuation of capivasertib.		**Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions.**
Sensitive substrates		**Sensitive substrates**
alfentanil	nisoldipine	budesonide
avanafil	quetiapine	buspirone
conivaptan	saquinavira	darifenacin
dronedarone	simvastatin	darunavira
eletriptan	sirolimus	ebastine
eplerenone	tacrolimus	felodipine
ivabradine	ticagrelor	indinavira
lomitapide	tolvaptan	maraviroc
lovastatin	triazolam	midazolam
lurasidone	vardenafil	sildenafil
naloxegol		tipranavira

Table 31. Drugs known to be sensitive or moderate sensitive CYP3A substrates whose exposure, pharmacological action, and toxicity may be increased by capivasertib	
Must be stopped 1 week prior to capivasertib administration. Must not be used concomitantly with capivasertib and for 1 week following discontinuation of capivasertib.	**Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions.**
Moderate sensitive substrates alprazolam atorvastatin eliglustat pimozide (+TdP risk)	**Moderate sensitive substrates** amlodipine aprepitant buprenorphine codeine colchicine fentanyl haloperidol methylprednisolone oxycodone rivaroxabanb sertraline tadalafil
[a] Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor. No clinically significant additional increase in exposure is expected by capivasertib when combined with ritonavir. [b] Rivaroxaban must not used concomitantly with both capivasertib and P-gp inhibitors. CYP= Cytochrome P450; TdP risk= Known risk of Torsades de Pointes according to the Arizona Centre for Education and Research on Therapeutics (ArizonaCert) website (https://www.crediblemeds.org/). Consider additional ECG monitoring.	

Table 32. Drugs known to be substrates for renal or hepatic transporters whose exposure, pharmacological action, and toxicity may be increased by capivasertib		
Drug	**Advice**	**Transporters involved**
dofetilide	Drug is permitted but caution should be exercised and participants monitored closely for possible drug interactions.	MATE1 and OCT2 substrate with a TdP risk
metformin	Metformin is currently the preferred oral anti-diabetic recommended for the management of hyperglycaemia occurring in participants enrolled in studies of capivasertib (see Section 6.3.4.2 for further guidance).	MATE, MATE-2K and OCT2
pitavastatin pravastatin rosuvastatin	Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions.	OATP1B1
procainamide	Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions.	OCT2 substrate with a TdP risk

* MERGEFORMAT

6.6.3.3 *Capivasertib Precautions Regarding QTc-prolongation Medications*

Due to the important potential risk of QT prolongation derived from the capivasertib non-clinical development programm, it is recommended that administration of any drugs (at screening or during study conduct) considered essential for patient management which are known to prolong

the QT interval is discussed with the Study PI (in consultation with AZ study physician, if indicated) and that consideration should be given for close monitoring of QT interval prolongation through frequent ECG and electrolyte monitoring. See **Table 31** for additional guidance regarding drugs known to prolong the QT interval and that are at risk for a potential pharmacokinetic interaction with capvasertib.

Please refer to the following sites for further information on inhibitors, inducers and substrates.

- https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
- https://didb.druginteractionsolutions.org/

6.6.4 SELUMETINIB

6.6.4.1 *Selumetinib Precautions Regarding CYP-interacting Medication*

Unless considered clinically indicated, participants should avoid changes to or the addition of concomitant medications that may affect the metabolism of selumetinib, including CYP2C19, or 3A4 moderate/strong inhibitors/ inducers (summarized in Appendix H). There are no dose reduction recommendations for selumetinib if these concomitant medication cannot be avoided.

During the studies, participants should avoid consuming large amounts of grapefruits, Seville oranges, or any other products that may contain these fruits (e.g., grapefruit juice) as these may effect selumetinib metabolism.

6.6.4.2 *Vitamin E intake*

Selumetinib capsules contain vitamin E in the form of TPGS, a water-soluble form of vitamin E, which acts as a formulation excipient. The maximum daily dose of vitamin E that a study subject may receive from selumetinib is approximately 261.6 mg/day. Therefore,-

- participants should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interfere with blood coagulation processes.
- Selumetinib should be administered with caution in participants who are also receiving concomitant coumarin anticoagulant medications (e.g. warfarin). These participants should have their INR monitored / anticoagulant assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

6.6.4.3 *Oral Hygeine*

Participants should be made aware of the need for good oral care while receiving selumetinib. Refer to Section 6.6.4.3.

6.6.5 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 below. 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.

6.6.5.1 *Ceralasertib Precautions Regarding CYP-interacting Medication*

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, 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. In vitro data also suggest that ceralasertib may be metabolised by CYP2C8 but a lesser extent, therefore caution should be applied with co administration of potent inhibitors or inducers of CYP2C8.

Potent inhibitors or inducers of CYP3A should not be combined with ceralasertib (refer to Appendix H). These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP3A or CYP2C8 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.

6.6.5.2 *Ceralasertib Precautions Regarding Pgp inhibitors/inducers and/or BCRP inhibitors*

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. Agents listed are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate Pgp activity or BCRP activity (refer to Appendix H).

6.6.5.3 *Ceralasertib Precautions Regarding OATP1B1 and BCRP Substrates*

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 (refer to Appendix H).

6.7 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

- The use of any natural/herbal products (including cannabis) or other traditional remedies should be discouraged, but the use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:
    - Reason for use
    - Dates of administration including start and end dates
    - Dosage information including dose and frequency
- Participants should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab.
- Live vaccines within 30 days prior to the first dose of study drug and while on study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid (oral) vaccine.

  - Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed. Vaccines for SARS-CoV-2 (i.e., COVID-19) are permitted.

- Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers.
- Drugs with laxative properties and herbal or natural remedies for constipation.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management may be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

Participant exclusion criteria (**Section 4.2**) describes other medications prohibited in this trial.

7. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

7.1 STUDY SPECIFIC PROCEDURES

7.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the participant's TNBC will be recorded separately and not listed as medical history.

7.1.2 DISEASE ASSESSMENT

The investigator or qualified designee will obtain prior and current details regarding the participant's breast cancer.

7.1.3 MEDICATION HISTORY

A complete medication history will be acquired concurrently with medical history.

7.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant, or Advanced Registered Nurse Practitioner as local law permits and per institutional standards. The physical examination to be conducted will include an evaluation of: general appearance; head, ears, eyes, nose, and throat; neck; skin; cardiovascular system; respiratory system; gastrointestinal system; lymphatic system, musculoskeletal system, and nervous system. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings. All physical examinations will also include:

7.1.4.1 *Vital signs*

Vitals to be collected include blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry. As part of the screening/baseline visit, vitals should be obtained within 10 days prior to the first dose of study agent. Vitals will also be obtained during treatment.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF page.

7.1.4.2 *Height and weight*

Height will be collected at screening only. Weight will be collected at each visit.

7.1.4.3 *Performance status*

Performance status will be determined for all participants at screening and at select times during treatment as per the assessment schedule in Section 7.14. Refer to Appendix C for performance criteria.

7.1.5 ELECTROCARDIOGRAM (ECG)

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the participant has been in a supine position and recorded while the participant remains in that position.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 10.1.1
At Screening, a single ECG will be obtained on which QTcF must be <470 ms.
In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
Situations in which ECG results should be reported as AEs are described in Section 9.1.

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules

7.1.5.1 *Selumetinib arm (only)*

An ECG assessment is not required if taken within 14 days of the screening ECG and the participant's condition has not changed (no new treatment during this period of time with no new complication or aggravation).

Single ECGs should be performed at the time of significant LVEF drop (Section 6.3.5.8) and on occurrence of any cardio respiratory adverse event with no obvious diagnosis. For patients with new or worsening respiratory symptoms (such as dyspnea, cough), an ECG is recommended and additionally at the discretion of the Investigator if clinically indicated.

7.1.5.2 *Capivasertib arm (only)*

For participants assigned to receive capivasertib, an ECG should be performed pre-dose and 1-2 hours post-dose on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and every 12 weeks thereafter, as clinically indicated, at end of treatment visit(s) and 30 days post last dose of capivasertib.

7.1.6 ECHOCARDIOGRAM (ECHO)/MULTI-GATED ACQUISITION (MUGA) SCAN

A baseline MUGA/ECHO should be performed at screening for all participants, and thereafter only as clinically indicated. For participants assigned to Arm 2 (selumetinib) or Arm 3 (capivasertib), additional scans are required as follows:

Arm 2 (selumetinib) –MUGA/ECHO assessment shoud be performed every 3 months while receiving selumetinib.

Arm 3 (capivasertib) - MUGA/ECHO assessment should be performed as clinically indicated while receiving capivasertib.

7.1.7 MEDICAL DIARY

Participants that self-administer oral study agents (e.g., olaparib) are required to maintain a medication diary to assess compliance. Participants will receive instruction on how to

administer study drug from a physician, clinical research nurse, or other designated, qualified healthcare provider. Participants will be provided with a medical diary and are required to record the date, dose, and the time of the ingestion.

7.1.8 ADVERSE EVENT EVALUATION

Toxicities and adverse experiences will be assessed at each visit using the NCI CTCAE 5.0. Safety will be monitored by assessing physical examination, vital signs, body height (screening only) and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, and pregnancy, as well as collecting of AEs at every visit.

Adverse events will be monitored from the time the participant receives treatment on study. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study, including and up to 3 months following completion of study therapy. All AEs (serious and non-serious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug.

Abnormal laboratory values will only be recorded as an AE if determined to be clinically significant by the investigator.

For details on AE collection and reporting, refer to Section 9.

7.1.9 EYE EXAMINATION (*SELUMETINIB TREATMENT ARM ONLY*)

For participants assigned to receive selumetinib, an ophthalmologic examination (best corrected visual acuity, intraocular pressure and slit lamp fundoscopy) should be performed at screening and as clinically indicated whilst the participant is on study drug.

If a participant experiences AE/symptoms of visual disturbance (including blurring of vision) a complete ophthalmological examination, including a slit-lamp examination, must be performed.

If an abnormality is detected, fundus photography and an OCT scan can also be performed where required. AEs are to be managed accordingly to Section 6.3.5.2. If retinal abnormality prior to or at the time of selumetinib discontinuation has been observed a repeat ophthalmological examination is to be performed 30 days after discontinuation of selumetinib in order to document reversibility.

7.2 **RADIOGRAPHIC OR OTHER IMAGING ASSESSMENTS**

Tumor imaging may be performed by computed tomography (CT) (preferred), magnetic resonance imaging (MRI), or Fluorodeoxyglucose (^{18}F)-positron emission tomography (PET) may be used if clinically indicated. Likewise, if clinically indicated, bone scans will also be utilized to assess osseous metastases. Plain X-ray evaluation may also be obtained for symptomatic sites with negative bone scan evaluations.

Radiographic imaging for disease assessment will follow standard of care and be performed according to institutional guidelines. Imaging should be performed according to Schedule of Events (Section 7.14); however, more frequent imaging is allowed if clinically indicated.

Initial tumor imaging must be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the

screening scan if they are of diagnostic quality, meet the requirements specified in the imaging manual, and performed within 28 days prior to the first dose of trial treatment.

After completing on-study therapy, the results of subsequent imaging assessments will be captured as part of study follow-up.

7.2.1 COMPUTED TOMOGRAPHY

Tumor imaging may be performed by CT, as clinically indicated, according to institutional guidelines.

7.2.2 MRI

MRI may be performed according to institutional guidelines.

7.2.3 BONE SCANS

^{99m}Tc -methylene diphosphonate (MDP) bone scintigraphy is not required. Participants with positive bone scans at baseline may be followed as clinically indicated with additional scans. A bone scan may be obtained for participants with new symptoms concerning of osseous metastasis (e.g., new persistently elevated alkaline phosphatase). Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations. New osseous uptake, upon confirmation with CT or per institutional standard, will be assessed for progression per RECIST 1.1. Lytic/mixed lesions with soft tissue component may be included in the evaluation of disease burden if it meets measurability criteria, while blastic lesions are considered non-measurable, in accordance with RECIST 1.1.

7.2.3.1 *Dose administration*

Dose administered should be according to standard weight-based protocols. Injection site should be away from lesion extremity or contralateral extremity if flow imaging is to be performed. Three-phase imaging is not required unless warranted by symptoms for a focal lesion to assess hyperemia.

7.2.3.2 *Imaging parameters*

Whole body delayed imaging is acquired 2-3 hours after injection of the radiopharmaceutical. Spot views should be acquired of specific sites of symptoms or of any sites of abnormality as warranted by the whole body views.

7.2.4 POSITRON EMISSION TOMOGRAPHY (PET)

^{18}F-PET imaging is optional but is encouraged for all participants. The primary lesion must be ≥ 1 cm on baseline anatomic imaging in order for an FDG-PET scan to be performed.

7.2.4.1 *Participant Guidelines*

The participant should fast for at least 4 hours prior to injection of ^{18}F. ^{18}F -PET imaging may follow a multi-gated acquisition scan (MUGA) study on the same day, or ^{18}F-PET imaging may be performed on the day preceding this study. Plasma glucose should be checked and, if the participant is hyperglycemic (plasma glucose > 250 mg/dL), appropriate treatment with small

doses of insulin may be given to bring the plasma glucose into the normal range prior to ^{18}F - PET imaging. However, insulin administration may result in excessive muscle uptake of ^{18}F and consequent tumor non-visualization. If possible, the study should be postponed until the plasma glucose is under better control.

Good hydration is required, as the primary route of ^{18}F excretion is renal. The participant should drink water or receive intravenous fluids (not containing dextrose) after ^{18}F injection to promote urinary excretion of the radioactive substrate. After injection, the participant must be kept in a resting state for 45-60 minutes prior to imaging. The participant should empty the bladder immediately prior to imaging.

7.2.4.2 *Imaging Technique*

The technique will vary by local institutional guidelines. In general, ^{18}F is administered intravenously at a dose of 0.125-0.200 mCi/kg or by algorithms that adjust the dose by body surface area, with a minimum total dose of 2.0 mCi and maximum total dose of 20.0 mCi.

The body should be imaged from the top of the ears to the bottom of the feet. If there is suspicion of involvement of the skull or skull contents, the volume that is imaged should be expanded.

Imaging with a dedicated PET/CT camera is standard.

The length of time needed to perform head to toe CT will depend on the participant's height but will be approximately 45 seconds. Contiguous axial images should be obtained at 5 mm thickness using 90 mA and 120 Kv and adjusted for local institutional protocol. No oral or IV contrast is required, but either or both are permissible and may be of benefit in cases where intraabdominal or pelvic pathology is a specific concern. With regard to participant positioning, the arms can be placed in a comfortable position at the participant's sides as long as they fit into the field of view. If the participant is large, it may be necessary to lay the arms across the abdomen and hold in position with a stabilizing device.

7.2.4.3 *Study Processing*

The ^{18}F-PET study is processed for display by an iterative reconstruction algorithm. ^{18}F activity should be corrected for attenuation, scatter, and radioactive decay. Attenuation correction is necessary, as apparent uptake will otherwise vary with depth of the lesion in the body and the nature of surrounding tissues. The procedure used for attenuation correction should be recorded. The level of tumor uptake is assessed subjectively by visual inspection and semi-quantitatively by determination of standardized uptake values (SUV). Uptake time, glucose levels, and partial volume effects influence both methods. The SUV method is also dependent on body weight, and correction of SUV by normalizing for body surface area (BSA) reduces this dependency on body weight. SUVs should be calculated for lesions known to be 1.2 cm or larger in diameter. Smaller lesions may have underestimated SUVs due to partial volume averaging effects at typical scanner resolutions (0.6-1.2 cm).

To calculate the SUV, a region of interest (ROI) should be carefully drawn around as much of the area of elevated ^{18}F uptake as can be done. The SUV should be calculated as SUVBSA = ROI activity concentration (nCi/cc) x BSA / injected activity (nCi). SUV_{MAX} is obtained by determining the activity of the pixel with the highest ^{18}F uptake.

7.3 LABORATORY PROCEDURES AND EVALUATIONS

Refer to Section 7.14 for a schedule of all laboratory test and procedures.

7.3.1 HEMATOLOGY

Hematologic profiling will be collected per institutional standards and should include evaluation of hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.

7.3.2 BIOCHEMISTRY

Blood chemistry will be collected per institutional standards and should include the following:

- Albumin
- Alkaline phosphatase[A]
- Alanine aminotransferase[A]
- Aspartate aminotransferase[A]
- Bicarbonate
- Calcium
- Chloride
- Creatinine
- Creatinine Phosphokinase[B]
- Glucose
- HbA1c[C]
- Total bilirubin[A]
- Serum or plasma troponin I or T[C]
- Serum or plasma lipids[C]
- Free T3 or free T4[D]
- Total protein
- Total cholesterol and triglycerides (fasted)[C]
- Magnesium
- Potassium
- Sodium
- Urea or blood urea nitrogen, depending on local practice
- Serum glucose (fasted)[C]

[A] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
In case a participant shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to 0 ' Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law (Appendix G), for further instructions
[B] Only required only for those receiving selumetinib, or as clinically indicated
[C] Only required only for those receiving capivasertib, or as clinically indicated
[D] Free T3 or free T4 should only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

For screening only (all participants): Hepatitis B (e.g., HBsAg reactive), Hepatitis C (e.g., HCV Ab, HCV RNA), and HIV (HIV antibody, HIV RNA) status. For individuals with controlled HIV, results of $CD4^+$ T-cell count and viral load derived from clinical reports in the past 3 months prior to study entry are acceptable. Amylase, Lipase, Lactate dehydrogenase.

For Arm 3 (capivasertib only) - total cholesterol and triglycerides (fasted): Total cholesterol and triglycerides (fasted) to be performed at screening and every 12 weeks thereafter, as clinically indicated, at end of treatment visit(s) and 30 days post last dose of capivasertib.

For Arm 3 (capivasertib only) – serum glucose (fasted): Serum glucose (fasted) to be performed at screening, pre-dose and 2 (+2) hours post-dose on Cycle 1 Day 1, pre-dose on Cycle 1 Day 15, pre-dose on Day 1 of each subsequent cycle, as clinically indicated, at end of treatment visit(s) and 30 days post last dose of capivasertib.

For Arm 3 (capivasertib only) – Serum glycosylated hemoglobin (HbA1c) to be performed at screening, and every 12 weeks thereafter and as clinically indicated.

7.3.3 TUMOR MARKERS

Carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA 15-3), and cancer antigen 27-29 (CA 27-29) will be collected as per the schedule of events (Section 7.14).

7.3.4 URINALYSIS

A baseline urinalysis should be performed at screening for all participants: color and appearance, glucose, protein, hemoglobin (blood), bilirubin, ketones, pH, and specific gravity. A microscopic exam should be performed for 2+ (~0.5 to 1.5 g/24 hours) or higher hemoglobin or protein levels.

For Arm 3 (capivasertib only) - urinalysis assessments to be performed at screening, Cycle 1 Day 1, Day 15, at Day 1 of each subsequent cycle, as clinically indicated, at end of treatment visit(s) and 30 days post last dose of capivasertib.

7.3.5 COAGULATION PANEL

Activated partial thromboplastin time (APTT) will be performed at screening and if clinically indicated.

International normalized ratio (INR) will be performed at screening and if clinically indicated. Participants taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.
Each coagulation test result will be recorded in the appropriate eCRF.

7.3.6 PREGNANCY TEST

Pregnancy tests on blood or urine samples will be performed for participants of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, on Day 1 of each subsequent treatment cycle, and at the 30 day follow up visit. Serum pregnancy test at time of screening is preferred, but urine test is acceptable. Tests will be performed by the hospital's local laboratory. If results are positive the participant is ineligible, and must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the participant's medical records.

7.3.7 BONE MARROW OR BLOOD CYTOGENETIC SAMPLES

Bone marrow or blood cytogenetic samples may be collected for participants with prolonged hematological toxicities, as defined in section 6.3.1.3.

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

7.4 BIOSPECIMEN COLLECTION

All bio-specimens will be given a specimen identification number generated by OHSU's approved Biobank Enterprise Management System (BEMS) (refer to Section 12.3.4) and, possibly a study identification number. Specimen tracking will occur within BEMS and the study records to maintain chain of custody. Biospecimens may be labeled with identifying information in order to generate clinical reports. All specimens BEMS identification numbers will be linked to a limited data set of clinical information with the only identifiers being dates of treatment, and participant age [date of birth] at time of treatment. In this study, clinical data and excess bio-specimens not distributed to research labs, as described in Appendix B will be stored for future research within the OHSU Biolibrary (refer to Section 12.3.5).

Archival tissue and any previous assay or test results may also be acquired for analysis. For the purposes of this protocol, archival tissue is defined as any biospecimen collected prior to enrollment on this study (e.g., at initial or recurrence diagnosis). Tissue may be from the primary site or metastases obtained during prior procedures. The archived tissue sample may be formalin fixed and paraffin embedded (FFPE) blocks on file within the local pathology department or may require requesting biospecimens from the outside facility that performed the initial diagnostic procedure.

7.4.1 TISSUE BIOPSY

All participants will have the required core biopsies taken pretreatment and at 2 weeks after starting olaparib monotherapy (cycle 1 day 14 ± 7 days) for CLIA assays and exploratory studies. A biopsy at the time of disease progression is optional, but not required. Biopsy procedures will be performed according to institutional guidelines and may be excisional, incisional, or core needle (image guided recommended). The investigator(s), in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Tumor biopsy should not be performed on Fridays, holidays, or the day before a 1 or 2-day holiday, or weekends. If overnight shipment is required, specimens must be shipped Monday-Thursday, except for holidays or the day before a holiday. Please refer to SMMART-AMTEC Laboratory Manual for shipping details.

For fresh tumor biopsies, 7 core biopsies from an 18 gauge needle (or an equivalent amount of tissue) are recommended. When possible, the tumor site biopsied should be different from any lesion that is being measured using RECIST v1.1 criteria. Depending upon tissue availability, additional core biopsies may be preserved in additional formats for optional exploratory research analytics (refer to Appendix B). Details regarding the appropriate labeling, handling, and shipping of specimens are detailed in the SMMART-AMTEC Laboratory Manual.

7.4.1.1 *Pre-treatment biopsy*

Pre-treatment tumor biopsy is required for all study participants. Pre-treatment biopsy may be done during the screening period prior to study treatment start.

7.4.1.2 *On-treatment Biopsy*

On-treatment tumor biopsy at 2 weeks is required for all study participants. Tissue biopsy must be collected on Day 14 of Cycle 1 (± 7days).

Note: If the biopsy at 2-weeks yields insufficient tumor cells for the effective evaluation of planned analytics, the participant may either:

1. Continue on the assigned therapy.
2. Proceed immediately with a second biopsy.
3. Go off study treatment and enter follow-up period (refer to Section 7.14).

7.4.1.3 *Optional core biopsy at disease progression*

Following disease progression, tissue samples are optional and will be acquired in the same way as the on-therapy biopsies from participants who have consented. If a surgical procedure is performed for a clinical indication or as part of a different research study, excess tumor tissue may be used for research purposes with the consent of the participant.

7.4.2 BLOOD COLLECTION FOR RESEARCH

Peripheral blood for hematology and serum biochemistry should be collected per institutional guidelines. In most cases, blood samples for research purposes will be drawn from participants scheduled to have venipuncture for routine clinical purposes. In some cases, when this is not possible, a research-only blood draw will be undertaken. For this protocol, up to approximately 60 mL of blood may be collected, dependent on participant's status, for exploratory or clinical analytic per instance. Details regarding the appropriate labeling, handling, and shipping of blood samples are detailed in the SMMART-AMTEC Laboratory Manual.

Blood will be collected at the time points outlined in the schedule of events (Section 7.14).

7.4.2.1 *Blood for Clinical Analysis*

Peripheral blood will be collected for analysis by targeted DNA or whole exome sequencing.

7.4.2.2 *Blood for Research Analytics*

Peripheral blood will be collected for exploratory research analytics (refer to Appendix B for additional details). Details regarding the specific amounts and tube types are detailed in the SMMART-AMTEC Laboratory Manual.

7.4.3 FECAL SAMPLE COLLECTION

i) Collection of Specimen(s)

Participants will be requested to collect a stool sample up to 48 hours prior to the scheduled office visit. This is an optional procedure, and participants' refusal will not impact their continued trial eligibility. Samples are to be collected at screening, before starting durvalumab and at the time of disease progression. Participants will be provided a labeled container for sample collection and given detailed instructions by a member of the study team on how to collect the sample. Participants will be instructed to not fill the biospecimen container more than three-quarters full (i.e., to the indicated line on the label of the container). Participants will be instructed to label the container with the date of collection, as well as any other information requested by the study team (e.g., diet requirements).

Biospecimens collected less than 4 hours prior to the scheduled visit can be stored at room temperature. Samples collected longer than 4 hours from the time of the visit must be stored at 4°C (maximum of 48 hours).

ii) Handling of Specimens
Specimens received from participants by the OHSU study team will be processed for DNA extraction and stored at -80°C until ready for analysis.

iii) Sites Performing Correlative Study
Knight Cancer Institute, Oregon Health & Science University; Portland, OR

7.5 SMMART CLINICAL ANALYTICS PLATFORM

The specific clinical analytics to be performed, under the SMMART Clinical Analytics Platform, on each participant sample will be dependent on sample availability and are subject to investigator discretion. All Laboratory Developed Tests (LDTs) or FDA-approved In Vitro Diagnostic (IVD) assays comprising the SMMART Clinical Analytics Platform will be performed by a CLIA-licensed/CAP-accredited laboratory. Potential clinical assays are detailed below. Unless otherwise stated, tumor tissue obtained from biopsies and peripheral blood will be routed through the KDL for appropriate processing and analysis of the described assays. At the discretion of the investigator, additional clinical assays not offered by OHSU may be requested from other CLIA-certified/CAP-accredited laboratories.

7.5.1 IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) staining of individual protein targets will be will be sub-contracted by the KDL to OHSU Surgical Pathology the Histopathology Shared Resource (HSR) or, if necessary, other CLIA-certified/CAP-accredited laboratories. IHC may be performed locally at each participating subsite and results provided to the OHSU coordinating center. The profiled proteins will relate to characteristics that are intrinsic to the cancer cells, such as growth, survival, death, motility, and DNA repair, as well as those that are extrinsic, such as the immune system and tumor microenvironment. Protein biomarkers to be assessed by IHC may include: estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), human epidermal growth factor receptor type 2 (HER2), markers of proliferation (Ki67), PD-L1, apoptotic regulators (BCL-2), GATA binding protein 3 (GATA3), cluster designated (CD) 4 (CD4), CD8, and phosphatase and tensin homolog (PTEN).

7.5.2 TARGETED DNA SEQUENCING

Sequencing of a targeted panel of genes to identify clinically relevant genetic alterations will be performed on patient biospecimen at the KDL using the GeneTrails® Solid Tumor Panel. The assay will also identify microsatellite instability (MSI) and may also report an estimate of the tumor mutational burden (TMB). Updated or alternative targeted panels may be used as they become available or if clinically appropriate.

7.5.3 WHOLE EXOSOME SEQUENCING

Whole exome sequencing (WES) of a tumor/normal pair to identify genetic alterations. The KDL will sub-contract WES to Tempus Labs, Inc., a CLIA-compliant/CAP-accredited laboratory (CLIA# 14D21140007 and CAP# 9457450). Tempus Labs, Inc. will perform high throughput sequencing, report the results back to the KDL, and provide raw sequencing files for download

and analysis. Alternatively, another CLIA-certified/CAP-accredited laboratory or research use only (RUO) service provider may be utilized at investigator discretion. Any results from a RUO service provider will not be used for clinical purposes or reported back to the participant.

7.5.4 RNA SEQUENCING

Sequencing of RNA isolated from patient biospecimen to characterize the transcriptome and identify fusions will be performed at the KDL or, if logistically necessary, another CLIA-certified/CAP-accredited laboratory. Regardless, processing of the raw sequencing data into gene-level expression values, including read alignment, recalibration, and quantification will be performed utilizing a computational pipeline constructed by the OHSU Bioinformatics Core and the KDL. Dependent upon sample availability, additional RNA sequencing work may be performed by Tempus Labs, Inc., who will provide raw sequencing files for download and analysis. In some cases, such as those with extremely limited sample availability, transcriptome sequencing may be replaced with a more limited RNA sequencing assay such as the GeneTrails® Solid Tumor Fusion Gene panel which identifies clinically actionable fusions in a limited set of genes.

7.5.5 PROTEIN PROFILING

Multiplex protein profiling to measure the abundance and phosphorylation status of proteins will be performed on patient biospecimen at the KDL. Profiling assays such as the GeneTrails® Quantitative Intracellular Signaling Panel or Nanostring® GeoMx Digital Spatial Profiler will be used to measure proteins related to characteristics intrinsic to the cancer cells, such as growth, survival, death, motility, and DNA repair. Additional or alternative protein profiling assays may be used as they become available.

7.6 SMMART EXPLORATORY RESEARCH ANALYTICS PLATFORM

The specific exploratory assays performed on each patient sample will be dependent on sample availability, relevance to the scientific objectives of this study, and are subject to investigator discretion. These analytics will be performed or overseen by OHSU scientists affiliated with the SMMART Clinical Trials Program. Potential exploratory assays comprising these exploratory research analytics are detailed in Appendix B.

OHSU scientists will conduct or oversee the analysis of clinical and exploratory assay results as well as the integration of these data with patient clinical metadata. In some instances, in order to accomplish their scientific objectives, OHSU scientists may work with internal or external collaborators or core facilities who provide essential expertise or capabilities. Study samples, data, or both may be released to co-investigators, collaborating institutions, and commercial laboratories for additional analyses aligned with achieving the aims of this study. All relevant policies and procedures for proper data and sample sharing will be followed, including requirements of de-identification of protected patient information or use of limited data set data.

7.7 QUALITY OF LIFE (QOL) AND PATIENT-REPORTED OUTCOMES (PRO)

Patient reported QOL will be assessed by two standard questionnaires, one for all cancer patients (QLQC30) and one specific to breast cancer (QLQBR23), both of which are recommended for inclusion in clinical trials in breast cancer patients.[175-177] QLQC30 will be used to describe participant QOL at baseline and to assess changes in response to study interventions. Utility of QLQBR23 has been demonstrated in several breast cancer clinical trials.

In a longitudinal study, metastatic breast cancer patients, completion rates for both surveys administered seven times over a 24-month period were >80% with these instruments detecting clinically meaningful worsening of symptoms over time.[178]

QLQC30 is a 30-item measure and yields scores for 5 functional scales (physical, role, cognitive, social, and emotional), 3-symptom scales (nausea, pain, and fatigue), a global health and QOL scale, and perceived financial impact of treatment.[179] QLQC30 can distinguish patients according to performance status and is the most commonly used QOL instrument in oncology research.[180,181]

QLQBR23 is a 23-item instrument that measures symptoms and side effects related to treatment, body image, sexuality, and future perspective specific to breast cancer patients. QLQBR23 has high internal consistency (Cronbach's a = 0.71-0.90), can distinguish between patients based on disease stage, performance status, treatment modality, or prior surgery, and is sensitive to change over time.[182]

QOL surveys will be collected at baseline and at times described in schedule of events.

7.8 SCREENING ASSESSMENTS

A screening (consultation) visit may occur as part of standard of care. If a participant is eligible for the study after a review of key inclusion/exclusion criteria, additional screening visits will be scheduled while staff members are requesting insurance review for exclusions to participate in a clinical trial.
The following will be reviewed at screening visit:

- Clinical history and physical exam (per standard of care)
- Informed consent obtained and documented
- Review of eligibility criteria
- Pre-treatment biopsy
- Screening assessments (see schedule of events in section 7.13)

Toxicities that occur prior to the start of treatment will not be subject to analysis. Demographic information, informed consent, and inclusion/exclusion information are the only data required for individuals who are screen failures.

7.9 BASELINE ASSESSMENTS

Baseline assessments should occur prior to the start of olaparib on Day 1 of Cycle 1. Participants will be evaluated for medical history, physical examination, vital signs, performance status, concomitant medications, blood sampling for hematology and laboratory tests, and any other specific assessments listed in Section 7.14, Schedule of Events.

7.10 ASSESSMENTS DURING TREATMENT

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Events (Section 7.13). Visits should occur on Day 1 of every cycle. Under certain circumstances (e.g., clinic holiday, inclement weather) scheduled visits may be delayed by no more than 3 days, or may occur earlier than scheduled by no more than 3 days during each treatment cycle cycles. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

7.11 EARLY TERMINATION OR END OF TREATMENT VISIT

Any participant that completes or discontinues treatment must be evaluated within 30 (+7) days after termination or prior to the initiation of any other off-study interventional therapy, if not performed within the last 30 days. End of treatment assessments are listed in Section 7.14, Schedule of Events.

7.12 FOLLOW-UP

Participants will be followed every 6 months (± 14 days) after removal from protocol therapy for a maximum of 1 year post-treatment. At a minimum, participants will be followed-up for disease status and survival. This information may be updated periodically via electronic health records, or follow-up contact may be made with the participant (by phone) or their treating physician to that end. Any follow-up visits will be consistent with standard of care, and assessments are listed in Section 7.14. Participants removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE.

A participant that discontinues the on-study assigned therapy due to progression, refusal, intolerable toxicity, desire for alternative non-protocol therapy, or other trials will be followed for disease and survival status.

7.13 UNSCHEDULED VISITS

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (e.g., laboratory or clinical assessments) at those visits should be recorded in the eCRF.

7.14 SCHEDULE OF EVENTS

Table 33. Study Dosing Schedule

Study agent	Cycle 1	Cycle 2+ (Days)																											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Olaparib[A]	**Days 1-28**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Durvalumab[B]	**-**	X																											
Selumetinib[C]	**-**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Capivasertib[D]	**-**	X	X	X	X				X	X	X	X				X	X	X	X				X	X	X	X			
Ceralasertib[E]	**-**	X	X	X	X	X	X	X	X	X	X	X	X	X	X														

[A] Olaparib is administered at a continuous dose of 300 mg PO BID for all 28 days of the treatment cycle (i.e., D1-28). For Cycle 2 onwards, olaparib is only administed to participants assigned to Arms 1, 2, and 3.
[B] Durvalumab (Arm 1 only) is administered as a 1500 mg IV infusion (every 4 weeks), on Day 1 of each cycle.
[C] Selumetinib (Arm 2 only) is administered at a continuous dose of 75 mg PO BID for all 28 days of the treatment cycle.
[D] Capivasertib (Arm 3 only) is administered at a dose 400 mg PO BID for 4 days with intermittent 3-day breaks in treatment
[E] Ceralasertib (Arm 4 only) is administered at a dose of 240 mg PO BID on Days 1 to 14 of each cycle.

Table 34. Planned study assessments

Visit Days (± 3 Days)*	Screening	Cycle 1		Cycle 2			Cycle 3-13	End of Treatment†	Follow-up‡
	Days -28 to -1	Day (D) 1**	D15	D1	D8§	D15	D1		
Informed consent	X								
Inclusion/exclusion criteria	X								
Prior/concomitant medications[A]	X	X	X	X		X	X	X	
Physical Examination[B]	X	X	X	X		X	X	X	X
Hematology[C]	X	X	X	X	X	X	X	X	X
Biochemistry[C]	X	X	X	X	X	X	X	X	X
Glucose (fasting)[Arm 3 only)]	X	X	X	X			X	X	X
Cholestrol (fasting)[Arm 3 only]	X	X	Every 12 weeks, or as clinically indicated					X	X
Tumor Markers	X	X		X		X	X	X	

Table 34. Planned study assessments

Visit Days (± 3 Days)*	Screening	Cycle 1		Cycle 2			Cycle 3-13	End of Treatment†	Follow-up‡
	Days -28 to -1	Day (D) 1**	D15	D1	D8§	D15	D1		
(CEA, CA 15-3, CA 27-29)									
TSH	X								
Coagulation	X								
Urinalysis	X	X Arm 3 only	X	X			X	X Arm 3 only	X Arm 3 only
ECG Arm 1, Arm 2, Arm 4	X	As clinically indicated – Refer to Section 7.1.5							
ECG Arm 3 only	X	X		X			ECG on Cycle 3 D1 – thereafter every 12 weeks or more frequent if clinically indicated		
MUGA/ECHO[D]	X	Arm 1, 3, and 4 – only as clinically indicated Arm 2 (selumetinib) – every 3 months while receiving selumetinib							
Pregnancy test[E]	X		X	X			X		
Medical Diary		X		X			X		
Mediport placement[F]	X								
Radiology[G]	X						X♦	X	X♦♦
AE assessment[H]	X	Continuously monitored							X
Fecal sample collection[I]	X		X	X				X	
Tumor tissue biopsy[J]	X		X[Δ]						X
Research blood samples[K]	X	X	X	X			X[K]	X•	
QOL Assessments[L]	X			At end of every 2nd treatment cycle				X	
Survival Outcomes		X	X	X		X	X	X	X

* Ideally, the clinic visit and all the study requirements should be performed on Day 1 of each cycle, but may be performed within 3 days before or after that day.
** Baseline visit should be conducted on Cycle 1 Day 1 prior to initiating study therapy, but may occur up to 3 days earlier.
† Participants deriving clinical benefit may, at the investigator's discretion, continue therapy.

Table 34. Planned study assessments

Visit Days (± 3 Days)*	Screening	Cycle 1		Cycle 2			Cycle 3-13	End of Treatment†	Follow-up‡
	Days -28 to -1	Day (D) 1**	D15	D1	D8§	D15	D1		

‡ Participants will be followed for up to 1 year post-treatment. Participants may be contacted by phone, and survival status will be collected and documented. Hematology and Biochemistry should be collected 30 days post last dose of study agent.

§ A visit on Day 8 during Cycle 2 is only required for participants receiving ceralasertib. Only hematology and biochemistry assessments are required at these visits. For participants receiving ceralasertib in Cycles 3 and subsequent treatment cycles, if thrombocytopenia is observed, then hematology and biochemistry assessments are required on Days 8 and 15 of each cycle.

A For concomitant medications – enter new medications started during the trial through the end of treatment visit.

B All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be collected at screening only.

C Hematology and biochemistry tests should be collected pre-dose on Day 1 of every 28-day cycle. Testing for HIV, HCV B, or C will only take place during screening.

D A baseline MUGA/ECHO should be performed at screening for all participants, and thereafter only as clinically indicated for Arms 1 and 4. For Arm 2 (selumetinib) only – a baseline ECHO is required is required prior to initiating selumetinib. Thereafter, an ECHO shoud be performed every 3 months while receiving selumetinib. For Arm 3 (capivasertib), only as clinically indicated.

E For women of reproductive potential, a serum (preferred) or urine pregnancy test should be performed within 14 days prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.

F Mediport placement is at the discretion of the investigator, and is to be installed at any time.

G Radiographic imaging will be conducted according to standard of care and follow institutional guidelines. Imaging modalities may include, but are not limited to, CT and/or MRI. The initial tumor imaging at screening will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. Measurable disease based on RECIST 1.1 must be confirmed by the investigator and/or radiologist.

H AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report grade 3 and 4 hem and non-hem SAEs (related and unrelated to trial treatment) occurring up until 90 days after the last dose of trial treatment, or the start of new anti-cancer treatment, whichever comes first. Afterward, report only SAEs that are related to trial treatment.

I This is an optional procedure, and participants' refusal will not impact their continued trial eligibility.

J Pre-treatment core biopsies are required prior to the initiation of protocol therapy. Samples obtained at the time of diagnosis before registration to this study may be submitted if they were collected within 3 months prior to the start planned study treatment. An additional, optional, tissue biopsy may be collected at time of disease progression.

K Research blood draws should be performed at time of pre-treatment Biopsy (if fresh tissue is collected), C1D1 (Baseline), C1D15, at time of on-treatment biopsy, C2D1, C3D1, C4D1, C6D1, End of Treatment visit, and at the time of the optional disease progression biopsy (if it occurs). Please refer to SMMART-AMTEC Laboratory Manual for additional details. For participants receiving durvalumab, research blood draws should occur prior to initiation of durvalumab infusion. On day-of-biopsy collections, it is highly preferred to collect research blood prior to tissue collection.

L QOL surveys (QLQBR23, QLQC30) will be collected at baseline, after completion of every two cycles of therapy and upon study completion or early termination.

♦ On-study radiographic imaging will follow standard of care and should occur every 2 months, or as clinically indicated.

♦♦ Post-treatment follow-up imaging will follow standard of care.

Δ The on-study tumor collection should occur after 2-weeks of starting olaparib monotherapy (i.e., Cycle 1 Day 14 [± 7]) days.

• Research blood collection may continue after completion of on-study treatment and will coincide with standard of care visits.

8. EFFICACY MEASURES

Tumor response will be determined per the investigators' assessment, according to RECIST v1.1 [183], and will be adapted using irRECIST[184] when evaluating disease progression to account for the unique tumor response characteristics associated with immunotherapy (i.e., Arm 1 only).

8.1 DEFINITION OF EFFICACY MEASURES

8.1.1 DISEASE PARAMETERS

Measurable disease. 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 as > 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

Non-measurable 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. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases 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.

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.

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.

8.2 DISEASE EVALUATION

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

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.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Use of MRI is also acceptable.

FDG-PET: Use of FDG-PET scanning to complement CT scanning may be utilized in the assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Cytology, Histology: Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases.

Tumor markers: Tumor markers (Section 7.3.3) alone cannot be used to assess response. This data will be collected but will not be used for the purpose of response evaluation.

8.3 EFFICACY CRITERIA FOR TUMOR RESPONSE

8.3.1 EVALUATION OF TARGET LESION

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.

8.3.2 EVALUATION OF NON-TARGET LESION

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 participant 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 principal investigator.

8.3.2.1 *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

8.3.3 OBJECTIVE RESPONSE RATE

The ORR is the proportion of participants that achieve a best overall CR or *Pr* (per RECIST v1.1

criteria). The best overall tumor response is assessed from the start of the combination study intervention until discontinuation of protocol-directed therapy (i.e., EOT). In cases of disease progression, the smallest measurements recorded since the start of treatment should be used as the reference. The best overall response for each participant evaluated during the course of this study depends on the findings of both target and non-target lesions, and also includes the occurrence of any new lesion (Table 35). Below is the summary table of overall response at a certain time point per RECIST guidelines.

Table 35. Best Overall Response: Participants with target ± non-target disease

Target Lesions	Non-Target Lesions	New Lesions	Best Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD or NE	No	*Pr*
CR	Not evaluated	No	*Pr*
Pr	Non-CR/non-PD or NE	No	*Pr*
SD	Non-CR/non-PD or NE	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

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

Note: Subjects 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

8.3.4 CLINICAL BENEFIT RATE

CBR is defined as the percentage of participants who have achieved complete response, partial response, and stable disease (i.e., CR + *Pr* + SD) for at least 6 months on study treatment.

8.3.5 DURATION OF RESPONSE

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. The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented. If a participant dies, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death will be used to denote the response end date.

Duration of stable disease: Stable disease is measured from the time of having completed at least one cycle of olaparib monotherapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

8.3.6 PROGRESSION-FREE SURVIVAL

PFS is defined as the time after having completed at least one cycle of olaparib monotherapy to

the first of either recurrence or relapse (anywhere in the body) or death at the time of last follow-up at 12-months.

8.3.7 OVERALL SURVIVAL

OS is defined as the time after having completed at least one cycle of olaparib monotherapy up to 6 months following the completion of on-study treatment to the date of death or last follow-up at 12 months.

8.4 **RESPONSE REVIEW**

Response assessment will be determined by the principal investigator.

8.5 **DEFINITION OF TUMOR RESPONSE USING IMMUNE RELATED RESPONSE CRITERIA (irRC)**

RECIST v1.1 criteria will be adapted to account for the unique tumor response characteristics associated with immunotherapy treatments such as durvalumab and will be used for sensitivity analysis (i.e., those assigned to Arm 1). Immunotherapeutic agents such as durvalumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as durvalumab.

irRECIST is identical to RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutics (e.g., durvalumab).[184] The assessment of unidimensional target lesions and response categories per irRC are identical to RECIST 1.1. Summary of measurements is as follows:

Measurable lesions:	≥10 mm in the longest diameter (5 lesions total, 2 per organ)
Measurement of each lesion:	The longest diameter (cm)
Sum of the measurements:	The sum of the longest diameters of all target lesions and new lesions (if any)

8.5.1 DEFINITION OF INDEX LESION RESPONSE USING IRRECIST

Complete Response (CR): Complete disappearance of all target and non-target lesions; Nodal short axis diameter <10 mm; No new lesions.

Partial Response (PR): Decrease, relative to baseline, of 30% in tumor burden relative to baseline; Non-unequivocal progression of non-target lesions; No new lesions.

Stable Disease (SD): Does not meet criteria for either CR or PR, in the absence of progressive disease.

irProgressive Disease (irPD): At least 20% (minimum 5 mm) increase in total measured tumor burden when compared with nadir or progression of non-target lesions or new lesions. Confirmation of progression requires two (2) consecutive observations at a minimum 4 weeks

(and maximum of 12 weeks) after the first irPD assessment. Where confirmed irPD includes new unequivocal progression or worsened progression from initial PD visit; appearance of another new lesion.

8.5.2 IMPACT OF NEW LESIONS ON IRRECIST

The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.

9. SAFETY

9.1 SPECIFICATION OF SAFETY PARAMETERS

The investigator is responsible for monitoring the safety of participants who have enrolled in the study. The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points, as described in Section 7.14, Schedule of Events. The investigator will follow any clinically significant adverse events persisting at the end of treatment visit until resolution/stabilization or death, whichever comes first.

9.2 DEFINITIONS

9.2.1 ADVERSE EVENT (AE)

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a participant's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment-emergent (i.e., occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the participant has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the participant being enrolled in the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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

9.2.2 SERIOUS ADVERSE EVENT (SAE)

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

- Death,
- A life-threatening adverse event,

- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or
- The development of drug dependency or drug abuse.

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

9.2.2.1 *New Malignancies On-study*

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

9.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

9.2.4 SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the CTCAE v5.0. In

the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

- **Mild** (grade 1) – An event that is usually transient in nature and generally not interfering with normal activities
- **Moderate** (grade 2) – An event that is sufficiently discomforting to interfere with normal activities
- **Severe** (grade 3) – An event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity
- **Life-threatening/debilitating** (grade 4) – An event that puts the participant at immediate or potential risk of death, requires hospitalization, or which drastically impacts a participant's well-being
- **Fatal** (grade 5)

9.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- *Definite* – The AE is clearly related to the study treatment.
- *Possible* – The AE may be related to the study treatment.
- *Unrelated* –The AE is clearly NOT related to the study treatment.

9.3 **EXPECTEDNESS**

The investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

9.4 **ADVERSE EVENT LIST(S)**

9.4.1 ADVERSE EVENT LIST FOR OLAPARIB

Refer to the current version of the Olaparib investigator brochure insert regarding detailed risks and expected AEs of olaparib. In brief, common AEs associated with olaparib include: rash (10% to less than 20%), constipation (22%), decrease in appetite (21% to 22%), diarrhea (21% to 33%), indigestion (up to 25%), nausea (58% to 76%), anemia, (all grades [23% to 44%]), leukopenia, (all grades [25%]), neutropenia (all grades [27%]), nasopharyngitis (up to 43%), respiratory tract infection (22% to 27%), and fatigue (46%). Serious AEs reported include: anemia (grade 3 or 4 [4% to 20%]), myeloid leukemia (Up to 2%), and pneumonitis (< 1%).

9.4.1.1 *Olaparib Adverse Events of Special Interest (AESI)*

AESIs 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. AESI for olaparib are the Important Identified Risk of MDS/AML and Important Potential Risks of new primary malignancy (other than MDS/AML), and pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study, there may be other events identified as

AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

9.4.2 ADVERSE EVENT LIST FOR DURVALUMAB

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus and diabetes insipidus, hypophysitis/hyperpituiarism, and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).

For information on all identified and potential risks with durvalumab, please always refer to the current version of the durvalumab IB.

Further information on these risks can be found in the current version of the durvalumab IB.
In monotherapy, clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, and decreased appetite. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicities (refer to separate durvalumab TMG).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

9.4.2.1 *Durvalumab Adverse Events of Special Interest*

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis/transaminase increases
- Endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis)

- Other inflammatory responses that are rare / less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (e.g., presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the separate Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by AZ to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

9.4.3 ADVERSE EVENTS LIST FOR CAPIVASERTIB

For information on all identified and potential risks with capivasertib please refer to the current version of the capivasertib IB. AEs observed with capivasertib (irrespective of causality) , include: diarrhea nausea vomitingstomatitisrashdry skinpuritishyperglycemiadecrease appetite and drug hypersensitivity

9.4.3.1 *Capivasertib Adverse Events of Special Interest*

Adverse events of special interest to be observed with capivasertib include:

- Hyperglycaemia
- Non-infectious diarrhea
- Pneumonia
- Rash
- Stomatitis
- Torsade de pointes/QT Prolongation

9.4.4 ADVERSE EVENTS LIST FOR SELUMETINIB

For information on all identified and potential risks with selumetinib please always refer to the current version of the selumetinib IB. In pooled data of monotherapy clinical studies (n = 347) selumetinib dosing, the observed AEs, irrespective of causality, include: dry skin (all grade, 57.2%), hair changes (all grade 6.1%), paronychia (all grade 2.6%), rashes (acneiform; all grade 49.6%; grade ≥ 3, 8.1%), and rashes (all grades, 67.7%, grade ≥3 10.4%), diarrhea (all grade, 48.1%; grade ≥ 3, 2.3%), nausea (all grade, 36.6%; grade ≥3, 1.7%, vomiting (all grade, 23.6%; grade ≥3, 2.3%), stomatitis (oral mucositis, all grade, 8.1%), dry mouth (all grade, 6.6%), asthenic events (all grade, 34.9%, grade ≥3, 5.8%), peripheral edema (all grade, 31.1%; grade ≥3, 1.2%), facial edema (all grade, 11.2%), pyrexia (all grade, 8.9%; grade ≥3, 0.9%), dyspnea (all grade, 16.4%; grade ≥3, 2.9%), vision blurred (all grade, 6.1%).

Kurnit et al[114] has preliminarily investigated the combination of olaparib and selumetinib. In early findings of 14 patients that received the treatment combination, the authors reported anemia and hypophosphatemia (any grade) as the most common AEs (additional AEs are described in **Table 36**)

Table 36. Kurnit et al., AEs reported with olaparib and selumetinib combination		
Adverse Event	**Any Grade**	**Grade 3**
Anemia	79%	
Hypophosphatemia	79%	
Acneiform Rash	71%	7%
Fatigue	64%	7%
Nausea	57%	
Diarrhea	50%	
Elevated aspartate aminotransferase	50%	7%
Oral mucositis	50%	
Dry mouth	43%	
Decreased white blood cell count	36%	7%
Dysgeusia	36%	
Elevated CPK	36%	7%
Other skin effects	36%	
Anorexia	29%	
Constipation	29%	
Dizziness	29%	
Dry skin	29%	
Edema	29%	
Elevated creatinine	29%	
Neutropenia	21%	7%
Decreased ejection fraction	14%	7%
Abdominal pain	7%	7%
Elevated bilirubin	7%	7%
Hepatic pain	7%	7%
Thromboembolic event	7%	7%

9.4.4.1 *Selumetinib Adverse Events of Special Interest*

Adverse events of special interest to be observed with selumetinib include:

- Ocular toxicity (Chorioretinopathy (central serous retinopathy [CSR]), Retinal detachment, Retinal tear, Vision blurred, Visual impairment, Vitreous floaters, Photopsia, Eye disorder, Photophobia, Retinal vein occlusion (RVO), Detachment of retinal pigment epithelium (Retinal pigment epithelial detachment [RPED]).
- Hepatotoxicity (Drug-induced liver injury, ALT increased, AST increased)
- Muscular toxicity (Blood creatine phosphokinase increased, Musculoskeletal pain, Muscular weakness, Myalgia, Rhabdomyolysis, Myoglobin blood increased, Myoglobin

urine present, Acute kidney injury, Myopathy)
- Cardiac toxicity (Ejection fraction decreased, edema peripheral, Peripheral swelling, Oedema, Left ventricular dysfunction, Ventricular dysfunction)

9.4.5 ADVERSE EVENTS LIST FOR CERALASERTIB

For information on all identified and potential risks with ceralasertib please always refer to the current version of the ceralasertib IB. The most common AEs (i.e., >15%) reported among patients with solid tumors receiving ceralasertib monotherapy includes: gastrointestinal disorders (61.5%). fatigue (38.5%), anemia (38.5%), musculoskeletal and connective tissue disorders (46.2%), infections and infestations (30.8%), respiratory, thoracic and mediastinal disorders (30.8%), and nervous system disorders (23.1%).

9.5 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of a UP, AE, or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate eCRF.
The following variables will be collected for each AE:
- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (definite, probable, unrelated)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:
- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 9.2.5
- Description of the SAE

All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.
The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days for AEs, and for SAEs, up to 30 days (for Arms 2, 3, and 4) or 90 days (for Arm 1) after the last dose of study drug or until the initiation of alternative anticancer therapy, whichever occurs first. Any SAE that occurs after treatment with alternative therapy will be reported only if the investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the CTCAE v5.0.

9.5.1 ADVERSE EVENTS AFTER THE 90 DAY FOLLOW-UP PERIOD

All SAEs will be reported, whether or not considered causally related to the investigational product or the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of study drug or until the initiation of alternative anticancer therapy. The investigator and/or AZ are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30-day follow-up period for olaparib, capivasertib, selumetinib, and ceralasertib, and 90-day follow-up period for durvalumab, should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow-up for overall survival if the participant has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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

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

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

9.6 **OVERDOSE**

9.6.1 OLAPARIB, SELUMETINIB, CAPIVASERTIB, AND CERALASERTIB

There is currently no specific treatment in the event of an overdose with olaparib, selumetinib,

capivasertib, and ceralasertib, and possible symptoms of overdose are not established. Each study agent must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Allowed Dose for each agent is as follows:

- Olaparib – 300 mg twice daily (tablet).
- Selumetinib – 75 mg twice daily (capsule)
- Capivasertib – 400 mg twice daily (tablet) 4 days on / 3 days off
- Ceralasertib – 240 mg twice daily (tablet)

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

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.
The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.
For overdoses associated with an SAE, the standard reporting timelines apply, see Section 9.7.
For other overdoses, reporting must occur within 30 days.

9.6.2 DURVALUMAB

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure unless otherwise specified in this protocol.

Any overdose of a study participant with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee. If the overdose results in an AE (see Section 9.2.1), the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example, death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 9.2.2). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

9.7 **REPORTING PROCEDURES**

9.7.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures, and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports

that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

9.7.2 MEDWATCH REPORTING

The Sponsor-investigator is required (per 21 CFR 312.32) to report AEs that meet certain criteria to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the investigational product.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500A, the Mandatory Reporting form (available here). A copy of Form FDA 3500A and supporting materials will be kept on file in the study regulatory binder.

The Sponsor-investigator will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:
- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-18-13868)

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

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com

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

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

9.7.3 REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy should be recorded on the pertinent eCRF and reported by the Investigator to the IRB. Pregnancy follow-up should be reported using the same form. Any SAE experienced during pregnancy must be reported.

If, while on study treatment, a participant's sexual partner becomes pregnant, the pregnancy and pregnancy outcomes must also be reported as described above. Consent to report information regarding the pregnancy should be obtained from the pregnant individual.

9.8 REPORTING OF DEATHS TO ASTRAZENECA

All deaths that occur during the study, or within the protocol-defined 30 days post-last dose of selumetinib, capivasertib, or ceralasertib (Arms 2, 3, and 4), or 90 days post-last dose of durvalumab (Arm 1) safety follow-up period must be reported to AstraZeneca as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as an SAE within **24 hours**. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE.

Deaths that occur following the protocol-defined 30-day post-last dose of selumetinib, capivasertib, or ceralasertib, or 90-day post-last-dose of durvalumab, safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the participant has been permanently withdrawn from the study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

9.9 STUDY STOPPING RULES

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected.
- Death suspected to be related to the study intervention.
- As indicated by statistical stopping rules in this protocol (Refer to Section 10.2.3.3).

10. STATISTICAL CONSIDERATIONS

Refer to Section 3.1, Description of the Study Design for a detailed description of the study design and endpoints.

10.1 ANALYSIS POPULATIONS

The safety analysis set includes all enrolled participants that receive at least one dose of study medications.

The efficacy analysis set includes all participants who receive at least one cycle of on-study treatment of olaparib in combination with durvalumab, selumetinib, capivasertib, or ceralasertib (based on treatment arm assignment), and have had their disease re-evaluated (i.e., at least 1-post baseline disease assessment).

10.2 DESCRIPTION OF STATISTICAL METHODS

10.2.1 GENERAL APPROACH

This is a multi-arm, open-label Phase II study to evaluate the efficacy of olaparib in combination with durvalumab, selumetinib, or capivasertib, or ceralasertib monotherapy to treat patients with metastatic TNBC.

10.2.2 ANALYSIS OF PRIMARY ENDPOINT(S)

Using the efficacy analysis set, the estimate of ORR will be measured independently for each treatment arm and reported with 95% exact confidence interval. Participants who, within their respective treatment arm, achieve a CR or a PR that is confirmed on a second scan at least 4 weeks later on the current protocol will be qualified as achieving a response and will count towards the ORR measurement.

10.2.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

10.2.3.1 *Safety Endpoint*

The incidence of having Grade 3+ acute toxicity will be determined for participants with TNBC that received at least one dose of olaparib and/or durvalumab, selumetinib, capivasertib, or ceralasertib. The 95% confidence interval will be reported with the point estimate of toxicity rate.

10.2.3.2 *Efficacy Endpoints*

An estimate of CBR will be measured independently for each treatment arm and reported with 95% exact confidence interval. Participants who, within their respective treatment arm, achieve a CR, PR, or SD for at least 6 months on the current protocol will be qualified as deriving benefit from therapy and will count towards the CBR measurement.

The estimated distribution of the PFS, OS, and DOR for each treatment will be plotted using Kaplan Meier curves and reported with median survival and 95% confidence intervals if available.

10.2.3.3 *Interim Analysis and Stopping Rules – Arm 1 (olaparib and durvalumab)*

The trial will enroll 15 participants in stage 1. If 2 or less out of 15 respond, this treatment arm will be closed due to futility. Otherwise, the treatment arm will continue until a total of 28 participants are enrolled. All participants enrolled in stage 1 (n=15) will need to complete at least 1 post-baseline disease restaging assessment before the interim analysis can be completed. After 15 evaluable participants, recruitment to this treatment arm will be paused until the interim analysis is completed. The proposed combination therapy for this treatment arm is considered promising and worth further investigation if there are 8 or more responses among 28 participants.

10.2.3.4 *Interim Analysis and Stopping Rules – Arm (olaparib in combination with selumetinib or capivasertib, or ceralasertib monotherapy)*

Each treatment arm will independently enroll 11 participants in stage 1. If <2 of 11 respond in a given treatment arm, then that treatment arm will be closed due to futility. Within each treatment arm, if ≥2, ~~but <5~~, of 11 participants respond, the respective treatment arm will continue until a total of 22 participants are enrolled to that arm. For Arms 2-4, all participants enrolled in stage 1 (n=11) will need to complete at least 1 post-baseline disease restaging assessment before the interim analysis can be completed. After 11 evaluable participants, recruitment to that specific treatment arm will be paused until the interim analysis is completed. The proposed combination therapy for treatment Arms 2 and-3 is considered promising and worth further investigation if there are 7 or more responses among 22 participants. For Arms 2 and 3 only, if at the time of the stage 1 interim analysis, there are ≥ 5 of 11 responders within a given treatment arm, then an expansion cohort for TNBC patients without the biomarker characteristics will be opened using a Simon' 2-stage design.

10.2.3.5 *Biomarker Negative Expansion Cohort (Arms 2 and 3 only)*

Each biomarker negative expansion cohorts will only open after enrollment in Arm 2 or Arm 3, respectively, is completed. There is no formal plan to compare each treatment arm with its corresponding biomarker negative arm.

Each biomarker negative treatment will independently enroll 9 participants in stage 1. If 1 or less of 9 participants responds, then the arm will be closed due to futility. If ≥2 of 9 participants respond, the the trial will continue on to stage 2 until a total of 19 participants are enrolled. The biomarker selection criteria for the respective arm will be considered unpromising if more than 5 responses are observed in 19 participants.

10.2.4 ANALYSIS OF EXPLORATORY ENDPOINTS

As data warrant, exploratory analysis may be performed on each exploratory objective listed below:

1. Examine response rates depending on tumor characteristics
2. Identify predictive biomarkers of sensitivity to therapy
3. Identify emerging mechanism of resistance to therapy tumor markers of emergence.
4. Determine changes in tumor cells induced by PARP inhibitors
5. Identify tumor markers suggestive of combinatorial therapy that could overcome resistance to therapy

The results of these exploratory analyses may be reported separately from the clinical study report (CSR). In general, descriptive statistics, histograms, and hierarchical clustering (e.g. heatmaps and PCA plots) will be conducted to assess data quality, distributions, detect outliers,

and to visualize cellular and molecular changes associated with study treatment. For multiplexing IHC, statistically significant differences in unpaired and paired data will be determined using Kruskal-Wallis and Wilcoxon-signed rank tests. False discovery rates will be estimated to control for multiple comparisons. Where relevant, results from assays will be described by mean, standard deviation (SD), minimal, and maximal values. Comparison of group variables may be assessed using nonparametric tests of independence (e.g., Chi-square test or Fisher's exact test).

10.2.4.1 *Analysis of Quality of Life Measures*

Patient reported QOL will be assessed by two standard questionnaires, one for all cancer patients (QLQC30) and one specific to breast cancer (QLQBR23). Utility of QLQBR23 has been demonstrated in several breast cancer trials.[175-177] In a longitudinal study, metastatic breast cancer patients, completion rates for both surveys administered seven times over a 24-month period were >80%.[178] QOL surveys will be collected at baseline, after completion of every two cycles of therapy and at study completion or early termination.

QLQC30 is a 30-item measure and yields scores for 5 functional scales (physical, role, cognitive, social, and emotional), 3-symptom scales (nausea, pain, and fatigue), a global health and QOL scale, and perceived financial impact of treatment.[179] QLQC30 can distinguish patients according to performance status and is the most commonly used QOL instrument in oncology research.[180,181] Data from the EORTC QLQ-C30 instrument will be scored as previously described by Aaronson et al.[185]

QLQBR23 is a 23-item instrument that measures symptoms and side effects related to treatment, body image, sexuality, and future perspective specific to breast cancer patients. QLQBR23 has high internal consistency (Cronbach's a = 0.71-0.90), can distinguish between patients based on disease stage, performance status, treatment modality, or prior surgery, and is sensitive to change over time.[182] The EORTC QLQ-BR23 data will be scored as described by the EORTC scoring manual.[186]

The QOL measures will be summarized and presented over time graphically using box and spaghetti plots, in addition to summary tables. Mixed effect model will be further used to analyze the longitudinal data. For each instrument, the analysis will include all cycles for which at least 25% of participants in each arm that have an assessment.

10.2.4.2 *Additional Analyses*

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in a stand-alone analysis plan document.

10.3 **SAMPLE SIZE, POWER, ACCRUAL RATE, AND STUDY DURATION**

10.3.1 SAMPLE SIZE AND POWER

10.3.1.1 *Arm 1 (olaparib and durvalumab)*

A two-stage analysis will be performed using a Simon 2-stage Minimax design. The null (Immune checkpoint blockade alone) and alternative (Durvalumab and Olaparib) hypotheses are: H_0: π = 0.15 and H_a: π = 0.35. For the primary endpoint, a total sample size of 28 participants will achieve 80 percent power to detect the overall response rate difference of 0.20 using the two-stage Minimax design with one-sided type I error =0.05. The trial arm will be terminated in stage I if 2 or less out of the first 15 participants respond. If the trial goes on to stage 2, a total of 28 participants will be studied. If the total number responding is less than or equal to 7, the drug is rejected.

10.3.1.2 *Arms 2-4 (olaparib and selumetinib, or capivasertib, or ceralasertib monotherapy)*

Fleming's two-stage design will be used.[187] The null (PARPi monotherapy) and alternative (olaparib and capivasertib, or selumetinib, or ceralasertib monotherapy) hypotheses are: H_0: π = 0.15 and H_a: π = 0.40 (refer to Section 3.1.1 for justification). For the primary endpoint, a total sample size of 22 participants will achieve 80 percent power to detect the overall response rate difference of 0.25 with one-sided type I error=0.05. In the first stage, 11 patients will be accrued. If there are 1 or fewer responses in these 11 participants, the study arm will be terminated in stage 1. Otherwise, 11 additional participants will be accrued for a total of 22. The null hypothesis will be rejected if 7 or more responses are observed in 22 participants. If there are 5 or more responses in 11 participants, the study will open expansion study with biomarker negative patients.

For the biomarker negative expansion cohort (Arms 2 & 3 only): A two-stage analysis will be performed using a Simon 2-stage Minimax design. The null (PARPi monotherapy) and alternative hypotheses are: H_0: π = 0.15 and H_a: π = 0.4 (refer to Section 3.1.1 for justification). For the primary endpoint, a total sample size of 19 participants will achieve 80 percent power to detect the overall response rate difference of 0.25 using the two-stage Minimax design with one-sided type I error =0.05. The trial arm will be terminated in stage I if 1 or less out of the first 9 participants respond. If the trial goes on to the stage 2, a total of 19 participants will be studied. The null hypothesis will be rejected if more than 5 responses are observed in 19 participants.

10.4 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points, as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. The sample size for each analysis will be clearly stated along with the reason for exclusion if any participant is excluded from the analysis due to missing data.

11. CLINICAL MONITORING

11.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN (DSMP)

All clinical trials at the Knight are required to have a Data and Safety Monitoring Plan (DSMP). This study is under the oversight of the Knight Cancer Institute's DSMC, as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data, and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

The OHSU Knight Cancer Institute's 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 Investigator and study team.

The Knight DSMC will review each protocol every 6 months, but may occur more often, if required, to review toxicity and accrual data (please refer to Knight DSMP for additional details on reporting and audit frequency). Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected AEs that have been reported; summary of all deaths occurring within 30 days of study intervention, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g., scans, laboratory values) will be provided upon request.

11.2 CLINICAL DATA & SAFETY MONITORING

The OHSU Investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all participating sites, and final analysis of study data.

If monitoring is required, per the Knight DSMP, then monitoring visits will be performed during the study to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, and that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements. In this case, details of monitoring activities, including the designation of assigned monitoring entities, the scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate TSMP.

In the absence of a formal monitoring plan, the Investigator may work with his/her study team to conduct and document internal monitoring of the study to verify the protection of human participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If, at any time, investigator noncompliance is discovered at participating sites, the investigator shall promptly either secure compliance or end the investigator's participation in the study.

Independent audits will be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

11.3 QUALITY ASSURANCE & QUALITY CONTROL

The investigational site will provide direct access to all trial-related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

All clinical trials at the Knight Cancer Institute are required to have a Data and Safety Monitoring Plan. All clinical work conducted under this protocol is subject to ICH GCP guidelines. This includes inspection of study-related records by the lead site, sponsor, its designee, or health authority representatives at any time.

QA audit activities will occur as detailed in the Knight institutional DSMP. All discrepancies, queries, deviations, observations, and findings of non-compliance will be compiled into a final audit report. The PI must review and assess each finding, and generate a response to the audit report that incorporates a Corrective and Preventative Action (CAPA) plan. The CAPA must analyze root cause(s) of noncompliance to determine the appropriate changes to correct and resolve issues and prevent a recurrence.

Quality Control (QC) activities will occur to monitor and ensure the safety of study participants and the validity and integrity of data. Monitoring will be a continuous, ongoing, and multifaceted process. This includes review by the Knight DSMC and IRBs, as well as internal data quality control, review, and evaluation. Site monitoring visits are central to this process and will include reporting to appropriate individuals with oversight responsibilities.

The sponsor-investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

12. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

12.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate electronic case report forms (eCRFs), and source documentation.

12.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited (Refer to Section 12.6). Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally-identifying information. Electronic files for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, all study databases will be de-identified and archived within the Knight Cancer Institute.

12.3 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant-specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) systems, that is an approved EDC system that has been reviewed by OHSU Security. To further preserve confidentiality, PHI in the EDC systems will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the databases are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database. Data from CLIA assays will be entered into the EDC by study personnel at OHSU.

12.3.1 LABKEY DATA MANAGEMENT

LabKey will serve as an integration point for clinical and research data in this study. The LabKey platform provides solutions for study data management, biological assay data, biological specimen information, flexible data integration, file sharing, and data visualization in a secure password-protected environment. Features of LabKey that protect participants' privacy and data security include:

- Physical Security: The LabKey instance is hosted by the OHSU Information Technology Group (ITG) on servers housed by the Advanced Computing Center (ACC), providing locked physical security.
- Electronic Security: The LabKey instance is housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.
- Controlled User Access: LabKey employs a group and role-based security model that enables researchers to implement "minimum necessary" data access for their research staff. Access is integrated with OHSU's network such that users who are also OHSU

employees are authenticated against their OHSU network credentials.
- Data Integrity: LabKey is managed in accordance with OHSU Information Security Directives by ACC staff, ensuring fidelity of database configuration and back-ups.

Clinical data will be obtained through the Oregon Clinical and Translational Research Institute (OCTRI) Research Data Warehouse (RDW) (IRB #4076), a repository of clinical data and laboratory results for OHSU patients and research subjects to be used for clinical research. Information and web links to scanned biospecimen images housed in Open Microcopy Environment (OMERO) database and research results from individual research labs will also be stored in LabKey.

All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 11.3, Quality Assurance & Quality Control.

12.3.2 OREGON CLINICAL AND TRANSLATIONAL RESEARCH INSTITUTE (OCTRI) RESEARCH DATA WAREHOUSE (RDW)

The OCTRI RDW is a data repository for clinical data at OHSU and is the designated repository Guardian responsible for ensuring that the data are received and released according to OHSU policy and its IRB approved repository protocol (IRB #4076). Responsibilities include executing a usage agreement each time data are released for research purposes; ensuring security and confidentiality of stored data; securing data distribution; and tracking acquisition and release of data. In addition to data created for clinical care purposes, the RDW also includes OHSU research operations data, publicly available data and research data submitted for storage and future use.

Features of the RDW that protect participants' privacy and data security include:

- Physical Security: The RDW is hosted by the OHSU ITG on servers housed by the ACC providing locked physical security.
- Electronic Security: The RDW is housed behind both the OHSU firewall and a second ACC firewall. The ACC’s architecture has been reviewed by the OHSU Office of Integrity and undergoes periodic internal security audits.
- Controlled User Access: RDW staff authentication is performed per OHSU Information Security Policies. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials. Only authorized OHSU RDW staff are allowed direct access to individual RDW data. All RDW staff with direct access to individual RDW data are approved Co-investigators or Study Staff on the OHSU IRB protocol for the OCTRI RDW. All RDW staff have undergone training on pertinent OCTRI RDW policies and procedures and pertinent OHSU policies and procedures Additional steps are taken as appropriate with identifying data (e.g., names, addresses) to ensure only the “minimum necessary” identifying data are visible to RDW staff.
- Data Integrity: the RDW is managed in accordance with OHSU Information Security Directives by ACC staff, ensuring fidelity of database configuration and back-ups. The ACC's architecture has been reviewed by the OHSU Office of Integrity and undergoes periodic internal security audits.

For this study, clinical information from OHSU’s electronic medical records system (EPIC),

specimen information from the Biolibrary, and results from the KDL Clinical Genomics Database (CGD) will be queried from OCTRI RDW. All queried information will be deposited into the study-specific Data Mart, a database schema housed within OCTRI RDW.

12.3.3 OPEN MICROSCOPY ENVIRONMENT (OMERO)

OMERO will serve as the central repository for biospecimen images in this study. OMERO is a secure password-protected platform allowing for the viewing, analyzing, and sharing of image files. Features of OMERO that protect participants' privacy and data security include:

- Physical Security: The OMERO instance is hosted by the OHSU Information Technology Group (ITG) on servers housed by the Advanced Computing Center (ACC), providing locked physical security.
- Electronic Security: The OMERO instance is housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.
- Controlled User Access: OMERO employs a group and role-based security model that enables researchers to implement "minimum necessary" data access for their research staff. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.
- Data Integrity: OMERO is managed in accordance with OHSU Information Security Directives by ACC staff, ensuring fidelity of database configuration and back-ups.

12.3.4 BIOSPECIMENS

Information about specimens collected, and associated clinical data will be stored with the BEMS software, LABVANTAGE. This platform is a secure, commercial off-the-shelf system that is hosted by OHSU's ITG.

12.3.5 FUTURE USE OF STORED BIOSPECIMENS

Because we are committed to making data and/or biospecimens from this study available to the broader research community to address scientific questions and/or to find new ways to prevent, detect, or treat cancer and other diseases, participants will be asked to consent to an optional procedure to allow left-over biospecimens and data, including genetic data, to be stored indefinitely in a repository and shared for future research. Additionally, the informed consent will describe to the participant that de-identified data, including genetic data and/or biospecimens may be deposited into publically-accessible scientific databases (also refer to section 12.6.1).

The biospecimens and data collected for this protocol may be shared with the following repositories or databases listed below. *Please note*: If a participant consents to participation in the "Molecular mechanisms of tumor evolution and resistance to therapy (MMTERT, IRB#16113)" protocol any biospecimens and data may be stored and analyzed under MMTERT (IRB#16113) indefinitely to address the scientific questions and/or development of biological tests related to cancer as described in MMTERT study protocol.

12.3.5.1 *The Breast Cancer Observational Study (BCOS, IRB# 22179)*

Biospecimens (i.e. blood and tumor) and associated data may be submitted to OHSU IRB# 22179 BCOS for future management in accordance with relevant terms of consent and

authorization. Details of any transferred materials will be documented in submission agreement(s). Biospecimens and associated data will be stored under this study indefinitely and further analyzed to address scientific questions and/or development of biological tests related to cancer.

12.3.5.2 *BioLibrary, A Tissue Repository (IRB# 4918)*

If the participant agrees, any remaining biospecimens (i.e., blood and tumor) and associated data may be may be submitted to IRB# 4918 OHSU BioLibrary for future management in accordance with relevant terms of consent and authorization. Details of any transferred materials will be documented in submission agreement(s). Samples and associated data will be stored in the KCI BioLibrary indefinitely and further analyzed to address scientific questions and/or development of biological tests related to cancer.

12.3.5.3 *Oregon Clinical and Translational Research Institute (OCTRI) Research Data Warehouse (RDW) (IRB# 4076)*

All data collected originally for research purposes in this study will be accompanied by a fully executed submittal agreement and appropriate IRB documents prior to deposition in the OCTRI RDW. This submittal agreement documents that providers of data to the OCTRI RDW agree to the stipulations of data submission, as specified in the RDW IRB protocol (IRB# 4076). Data providers remain the steward of the data. (refer to Section 12.3.2 for further description of OCTRI RDW)

12.3.5.4 *Publically-Accessible Scientific Databases*

The informed consent option for storing samples for future research describes that their samples, data and genetic data from this study may be shared with others or placed into one or more publicly-accessible scientific databases, such as the NIH Database for Genotypes and Phenotypes (dbGaP). Any personal information that could identify a participant will be removed or changed before it is shared with other researchers or results are made public. We will seek to share or deposit de-identified data into publicly-accessible central repositories or databases that may be open or controlled access. Study data including genomic data will be de-identified according to the standards set forth in the HHS Regulations for the Protection of Human Subjects to ensure that the identities of research subjects cannot be readily ascertained with the data before it is submitted.

12.4 MAINTENANCE OF RECORDS

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results, and medication inventory records, must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed-upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

12.5 MULTICENTER GUIDELINES

Collaborating research subsites may be invited to participate in this study. In such cases, OHSU will serve as the coordinating center and will manage trial data in the following ways:

a. Confirm that all sites have received and are using the most recent version of the protocol. The protocol must not be rewritten or modified by anyone other than the OHSU Investigator. Documentation of the version that was sent to the site must be kept in the regulatory binders.
b. Confirm that the protocol and informed consent form have local IRB approval at each site prior to registration of the first participant. Documentation of IRB approval from other sites for continuing review must be submitted and kept in the binder.
c. Provide centralized participant registration in the clinical research management system.
d. Ensure collection and review of applicable source documents and case reports by the OHSU Investigator to ensure protocol compliance.
e. Maintain documentation for all SAE reports and submit regular summaries of all AEs, SAEs, and UPs from all sites to the Knight DSMC per DSMC requirements.
f. Ensure that relevant IRB correspondence and study status changes are communicated to all participating sites within 5 business days. Any changes that affect participant safety of study enrollments will be communicated immediately.
g. Submit documentation to the FDA such as protocol amendments, annual reports, and safety reports for unexpected, fatal or life-threatening events that are associated with the use of the investigational product.
h. Participating sites must submit regulatory documents including, but not limited to the following:
    - Current CV (signed and dated) for each Investigator.
    - Current medical license number for physician investigators.
    - Current signed FDA Form 1572.
    - Certificate of completion of institution-required human participant training course, the NIH online training in the protection of human research participants or other appropriate training.
    - Documentation of institutional Conflict of Interest.
i. IRB-approved site-specific ICF (must be reviewed and approved by OHSU Investigator and study team prior to submission to the local IRB.
j. All IRB-approved documents and approval memos.
k. Site delegation of authority and signature log.
l. Site DSMP.
m. Completed eCRFs (data entry) within 10 business days of study visit.

12.6 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

1. This study will comply with the NIH Public Access Policy, as applicable, to ensure that the public has access to the published results of NIH funded research.
2. This study will adhere to the requirements set forth by the FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment. The study record in both the NCI's Clinical Trials Reporting Program and

ClinicalTrials.gov should be maintained every 6 months and verified for accuracy until completion. In compliance with FDAAA and NIH policy, the primary outcome results of this trial will be reported to within 12 months of primary completion date. That is, primary outcomes reporting will occur 12 months after the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome. For trials that have more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Authors included in the publication of findings from this trial must have participated in the work and take public responsibility for appropriate portions of the content.

12.6.1 BIOSPECIMEN AND DATA SHARING POLICY

Data and/or biospecimens from this study may be made available to the broader research community while protecting the privacy and confidentiality of participants. The IRB-approved informed consent describes to the participant that their biospecimens, data and genetic data from this study may be shared with others or placed into one or more publicly-accessible scientific databases, such as the NIH Database for Genotypes and Phenotypes (dbGaP). Any personal information that could identify a participant will be removed or changed before it is shared with other researchers or results are made public. The study may share or deposit de-identified data into publicly-accessible central repositories or databases that may be open or controlled access. Study data including genomic data will be de-identified according to the standards set forth in the HHS Regulations for the Protection of Human Subjects to ensure that the identities of research subjects cannot be readily ascertained with the data before it is submitted.

Refer to Section 12.3.5 for details describing potential future use of stored specimens and data. Additionally, biospecimens and associated clinical data will be shared with investigators of an on-going, OHSU, prospective observational study, MMTERT (IRB#16113)", provided they are consented to IRB# 16113.

Per the discretion of the Principle Investigator, study data and/or biospecimens may be released to co-investigators, collaborating institutions, and commercial laboratories for research that will help achieve the aims of this study. Investigators outside OHSU are required to sign an appropriate agreement (e.g., data use agreement, material transfer agreement, research collaborative agreements) as determined by the Technology Transfer & Business Development (TTBD) office per OHSU policy and undergo review for potential commercial or intellectual property interests. Identified data from this study will not be released to non-OHSU investigators without appropriate IRB approval and HIPAA authorization.

Participants will not have access to experimental research data. Results of clinically validated tests may be obtained by request via the study investigator or treating physician.

12.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the

design and conduct of this trial. Conflicts of interest, for all study group members, should be disclosed and managed according to OHSU's established policies and procedures.
Refer to link: https://o2.ohsu.edu/integrity-department/conflict-of-interest/index.cfm

13. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312 (for IND studies), ICH E6, and applicable regulatory requirements for protection of patient data.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the local IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the local IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

13.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. It is possible that this information may be presented to potential participants via in-person or telephone conversations with a member of the study team. Potential participants will have the opportunity to review and discuss the study information with a member of the study team before signing the consent documents. The document consent form may be completed in person, through mailed correspondence, or electronically in which the participant can provide a scanned or photographed version of their signed consent form. The consent may also be signed electronically. Regardless, each new participant will be provided with a copy of the signed consent form and associated study document(s) for their own records. The copy can be provided through electronic communication (e.g., email address provided by the participant) or a hard copy (provided in-person or via pre-paid mail). The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by

emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

13.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and local IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB (and sponsor/FDA if under an IND) within 5 business days after the implementation.

An Investigator who holds an IND application must also notify the FDA of changes to the protocol per 21 CFR 312, respectively.

14. REFERENCES

1. Petkov, V.I.*, et al.* Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. *NPJ Breast Cancer* **2**, 16017 (2016).
2. Howlader, N.*, et al.* US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst* **106**(2014).
3. Anders, C.K. & Carey, L.A. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. *Clin Breast Cancer* **9 Suppl 2**, S73-81 (2009).
4. Early Breast Cancer Trialists' Collaborative, G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *The Lancet* **365**, 1687-1717 (2005).
5. Soni, A.*, et al.* Breast cancer subtypes predispose the site of distant metastases. *Am J Clin Pathol* **143**, 471-478 (2015).
6. Gong, Y., Liu, Y.R., Ji, P., Hu, X. & Shao, Z.M. Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study. *Sci Rep* **7**, 45411 (2017).
7. Foulkes, W.D., Smith, I.E. & Reis-Filho, J.S. Triple-negative breast cancer. *N Engl J Med* **363**, 1938-1948 (2010).
8. Carey, L., Winer, E., Viale, G., Cameron, D. & Gianni, L. Triple-negative breast cancer: disease entity or title of convenience? *Nat Rev Clin Oncol* **7**, 683-692 (2010).
9. Burstein, M.D.*, et al.* Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. *Clin Cancer Res* **21**, 1688-1698 (2015).
10. Lehmann, B.D.*, et al.* Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest* **121**, 2750-2767 (2011).
11. Dent, R.*, et al.* Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res* **13**, 4429-4434 (2007).
12. Kassam, F.*, et al.* Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. *Clin Breast Cancer* **9**, 29-33 (2009).
13. Mayer, I.A., Abramson, V.G., Lehmann, B.D. & Pietenpol, J.A. New strategies for triple-negative breast cancer--deciphering the heterogeneity. *Clin Cancer Res* **20**, 782-790 (2014).
14. Bayraktar, S.*, et al.* Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations. *Breast Cancer Res Treat* **130**, 145-153 (2011).
15. Rottenberg, S.*, et al.* High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci U S A* **105**, 17079-17084 (2008).
16. Hay, T.*, et al.* Poly(ADP-Ribose) Polymerase-1 Inhibitor Treatment Regresses Autochthonous Brca2/p53-Mutant Mammary Tumors In vivo and Delays Tumor Relapse in Combination with Carboplatin. *Cancer Research* **69**, 3850-3855 (2009).
17. Fong, P.C.*, et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* **361**, 123-134 (2009).
18. Isakoff, S.J.*, et al.* TBCRC009: A Multicenter Phase II Clinical Trial of Platinum Monotherapy With Biomarker Assessment in Metastatic Triple-Negative Breast Cancer. *J Clin Oncol* **33**, 1902-1909 (2015).
19. Helleday, T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Molecular oncology* **5**, 387-393 (2011).

20. Murai, J.*, et al.* Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Res* **72**, 5588-5599 (2012).
21. Pilié, P.G., Tang, C., Mills, G.B. & Yap, T.A. State-of-the-art strategies for targeting the DNA damage response in cancer. *Nat Rev Clin Oncol* **16**, 81-104 (2019).
22. Ashworth, A. A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. *J Clin Oncol* **26**, 3785-3790 (2008).
23. Robson, M., Goessl, C. & Domchek, S. Olaparib for Metastatic Germline BRCA-Mutated Breast Cancer. *N Engl J Med* **377**, 1792-1793 (2017).
24. Litton, J.K. A phase 3 study of the oral PARP inhibitor talazoparib (BMN 673) in BRCA mutation subjects with advanced breast cancer (EMBRACA). in *SABCS* (San Antonio, TX, 2017).
25. Tutt, A.*, et al.* Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* **376**, 235-244 (2010).
26. Kaufman, B.*, et al.* Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* **33**, 244-250 (2015).
27. de Bono, J.*, et al.* Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline BRCA1/2 Mutations and Selected Sporadic Cancers. *Cancer Discov* **7**, 620-629 (2017).
28. Sandhu, S.K.*, et al.* The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. *Lancet Oncol* **14**, 882-892 (2013).
29. Dunn, G.P., Old, L.J. & Schreiber, R.D. The three Es of cancer immunoediting. *Annu. Rev. Immunol.* **22**, 329-360 (2004).
30. Keir, M.E., Butte, M.J., Freeman, G.J. & Sharpe, A.H. PD-1 and its ligands in tolerance and immunity. *Annu. Rev. Immunol.* **26**, 677-704 (2008).
31. Okazaki, T. & Honjo, T. PD-1 and PD-1 ligands: from discovery to clinical application. *International immunology* **19**, 813-824 (2007).
32. Qin, A., Coffey, D.G., Warren, E.H. & Ramnath, N. Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. *Cancer Medicine* **5**, 2567-2578 (2016).
33. Pardoll, D.M. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* **12**, 252-264 (2012).
34. Brahmer, J.R.*, et al.* Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. *The New England journal of medicine* **366**, 2455-2465 (2012).
35. Hirano, F.*, et al.* Blockade of B7-H1 and PD-1 by Monoclonal Antibodies Potentiates Cancer Therapeutic Immunity. *Cancer Research* **65**, 1089-1096 (2005).
36. Iwai, Y.*, et al.* Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A* **99**, 12293-12297 (2002).
37. Okudaira, K.*, et al.* Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model. *Int J Oncol* **35**, 741-749 (2009).
38. Topalian, S.L.*, et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* **366**, 2443-2454 (2012).
39. Zhang, C.*, et al.* Anti-tumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. *Cytotherapy* **10**, 711-719 (2008).
40. Powles, T.*, et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* **515**, 558-562 (2014).

41. Rizvi, N.A.*, et al.* Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology* **33**, 8032-8032 (2015).
42. Segal, N.H.*, et al.* Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. *Journal of Clinical Oncology* **33**, 3011-3011 (2015).
43. Alexandrov, L.B.*, et al.* Signatures of mutational processes in human cancer. *Nature* **500**, 415-421 (2013).
44. Fife, B.T. & Bluestone, J.A. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunological reviews* **224**, 166-182 (2008).
45. Mellman, I., Coukos, G. & Dranoff, G. Cancer immunotherapy comes of age. *Nature* **480**, 480-489 (2011).
46. Palucka, A.K. & Coussens, L.M. The Basis of Oncoimmunology. *Cell* **164**, 1233-1247 (2016).
47. Taube, J.M.*, et al.* Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med* **4**, 127ra137 (2012).
48. Dong, H.*, et al.* Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* **8**, 793-800 (2002).
49. Topalian, S.L., Drake, C.G. & Pardoll, D.M. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol* **24**, 207-212 (2012).
50. Reck, M.*, et al.* Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* **375**, 1823-1833 (2016).
51. Weber, J.S.*, et al.* Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* **16**, 375-384 (2015).
52. Motzer, R.J.*, et al.* Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* **373**, 1803-1813 (2015).
53. Haricharan, S., Bainbridge, M.N., Scheet, P. & Brown, P.H. Somatic mutation load of estrogen receptor-positive breast tumors predicts overall survival: an analysis of genome sequence data. *Breast Cancer Res Treat* **146**, 211-220 (2014).
54. Nanda, R.*, et al.* Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. *J Clin Oncol* **34**, 2460-2467 (2016).
55. Adams, S. Phase 2 study of pembrolizumab as first-line therapy for PD-L1–positive metastatic triple-negative breast cancer (mTNBC): Preliminary data from KEYNOTE-086 cohort B. . in *ASCO* (Chicago, 2017).
56. Adams, S. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. . in *ASCO* (Chicago, 2017).
57. Schmid, P. Atezolizumab in metastatic TNBC (mTNBC): Long-term clinical outcomes and biomarker analyses in *AACR* (Washington, D.C, 2017).
58. Adams, S. Safety and clinical activity of atezolizumab (anti-PDL1) in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer. *Cancer Res* **76**(2016).
59. Taube, J.M.*, et al.* Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res* **20**, 5064-5074 (2014).
60. Tumeh, P.C.*, et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* **515**, 568-571 (2014).

61. Herbst, R.S.*, et al.* Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* **515**, 563-567 (2014).
62. Pfirschke, C.*, et al.* Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy. *Immunity* **44**, 343-354 (2016).
63. Galluzzi, L., Buque, A., Kepp, O., Zitvogel, L. & Kroemer, G. Immunogenic cell death in cancer and infectious disease. *Nat Rev Immunol* **17**, 97-111 (2017).
64. Kroemer, G., Galluzzi, L., Kepp, O. & Zitvogel, L. Immunogenic cell death in cancer therapy. *Annu Rev Immunol* **31**, 51-72 (2013).
65. Adams, S.*, et al.* Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol* **32**, 2959-2966 (2014).
66. Ali, H.R.*, et al.* Association between CD8+ T-cell infiltration and breast cancer survival in 12,439 patients. *Ann Oncol* **25**, 1536-1543 (2014).
67. Denkert, C.*, et al.* Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. *J Clin Oncol* **33**, 983-991 (2015).
68. Miyashita, M.*, et al.* Prognostic significance of tumor-infiltrating CD8+ and FOXP3+ lymphocytes in residual tumors and alterations in these parameters after neoadjuvant chemotherapy in triple-negative breast cancer: a retrospective multicenter study. *Breast Cancer Res* **17**, 124 (2015).
69. Dieci, M.V.*, et al.* Prognostic value of tumor-infiltrating lymphocytes on residual disease after primary chemotherapy for triple-negative breast cancer: a retrospective multicenter study. *Ann Oncol* **25**, 611-618 (2014).
70. Stewart, R.*, et al.* Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody. *Cancer Immunol Res* **3**, 1052-1062 (2015).
71. Narwal, R., Roskos, L.K. & Robbie, G.J. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus. *Clinical pharmacokinetics* **52**, 1017-1027 (2013).
72. Ng, C.M., Lum, B.L., Gimenez, V., Kelsey, S. & Allison, D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. *Pharmaceutical research* **23**, 1275-1284 (2006).
73. Wang, D.D., Zhang, S., Zhao, H., Men, A.Y. & Parivar, K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. *Journal of clinical pharmacology* **49**, 1012-1024 (2009).
74. Zhang, S., Shi, R., Li, C., Parivar, K. & Wang, D.D. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. *Journal of clinical pharmacology* **52**, 18-28 (2012).
75. Costa, R.L.B., Han, H.S. & Gradishar, W.J. Targeting the PI3K/AKT/mTOR pathway in triple-negative breast cancer: a review. *Breast Cancer Research and Treatment* **169**, 397-406 (2018).
76. Cossu-Rocca, P.*, et al.* Analysis of PIK3CA mutations and activation pathways in triple negative breast cancer. *PLoS ONE* **10**(2015).
77. Ooms, L.M.*, et al.* The Inositol Polyphosphate 5-Phosphatase PIPP Regulates AKT1-Dependent Breast Cancer Growth and Metastasis. *Cancer Cell* **28**, 155-169 (2015).
78. Pascual, J. & Turner, N.C. Targeting the PI3-kinase pathway in triple-negative breast cancer. *Annals of Oncology* **30**, 1051-1060 (2019).
79. Liu, H.*, et al.* Identifying and targeting sporadic oncogenic genetic aberrations in mouse models of triple-negative breast cancer. *Cancer Discovery* **8**, 354-369 (2018).
80. Baselga, J.*, et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *New England Journal of Medicine* **366**, 520-529 (2012).

81. Baselga, J.*, et al.* Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology* **18**, 904-916 (2017).
82. Hirai, H.*, et al.* MK-2206, an allosteric akt inhibitor, enhances antitumor efficacy by standard chemotherapeutic agents or molecular targeted drugs in vitro and in vivo. *Molecular Cancer Therapeutics* **9**, 1956-1967 (2010).
83. Hoeflich, K.P.*, et al.* The PI3K inhibitor taselisib overcomes letrozole resistance in a breast cancer model expressing aromatase. *Genes Cancer* **7**, 73-85 (2016).
84. Kim, S.B.*, et al.* Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Oncology* **18**, 1360-1372 (2017).
85. Mayer, I.A.*, et al.* A Phase Ib Study of Alpelisib (BYL719), a PI3Ka-Specific Inhibitor, with Letrozole in ERþ/HER2 Metastatic Breast Cancer. *Clinical Cancer Research* **23**, 26-34 (2017).
86. Schmid, P.*, et al.* A phase II, double blind, randomised, placebo-controlled study of the AKT inhibitor AZD5363 in combination with paclitaxel in triple-negative advanced or metastatic breast cancer (TNBC)(NCT02423603). *Cancer Res* **76**, 8-12 (2016).
87. Kumar, A., Fernadez-Capetillo, O. & Carrera, A.C. Nuclear phosphoinositide 3-kinase β controls double-strand break DNA repair. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 7491-7496 (2010).
88. Ibrahim, Y.H.*, et al.* PI3K inhibition impairs BRCA1/2 expression and sensitizes BRCA-proficient triple-negative breast cancer to PARP inhibition. *Cancer Discovery* **2**, 1036-1047 (2012).
89. Juvekar, A.*, et al.* Combining a PI3K Inhibitor with a PARP Inhibitor Provides an Effective Therapy for BRCA1-Related Breast Cancer. *Cancer Discovery* **2**, 1048-1063 (2012).
90. Matulonis, U.A.*, et al.* Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. *Ann Oncol* **28**, 512-518 (2017).
91. Westin, S.N.*, et al.* Phase I trial of olaparib (PARP inhibitor) and vistusertib (mTORC1/2 inhibitor) in recurrent endometrial, ovarian and triple negative breast cancer. *Journal of Clinical Oncology* **36**, 5504-5504 (2018).
92. Michalarea, V.*, et al.* Abstract CT323: Accelerated phase I trial of two schedules of the combination of the PARP inhibitor olaparib and AKT inhibitor AZD5363 using a novel intrapatient dose escalation design in advanced cancer patients. *Cancer Research* **75**, CT323-CT323 (2015).
93. Westin, S.*, et al.* Phase I expansion of olaparib (PARP inhibitor) and AZD5363 (AKT inhibitor) in recurrent ovarian, endometrial and triple negative breast cancer [ESMO abstract 391P]. *Annals of Oncology* **28**(2017).
94. Jones, R.H.*, et al.* Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. *The Lancet Oncology* **21**, 345-357 (2020).
95. Dhillon, A.S., Hagan, S., Rath, O. & Kolch, W. MAP kinase signalling pathways in cancer. *Oncogene* **26**, 3279-3290 (2007).
96. Cerami, E.*, et al.* The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. (AACR, 2012).

97. Craig, D.W.*, et al.* Genome and transcriptome sequencing in prospective metastatic triple-negative breast cancer uncovers therapeutic vulnerabilities. *Molecular Cancer Therapeutics* **12**, 104-116 (2013).
98. Koboldt, D.C.*, et al.* Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61-70 (2012).
99. Turashvili, G.*, et al.* Novel prognostic and predictive microRNA targets for triple-negative breast cancer. *The FASEB Journal* **32**, 5937-5954 (2018).
100. Saini, K.S.*, et al.* Targeting the PI3K/AKT/mTOR and Raf/MEK/ERK pathways in the treatment of breast cancer. *Cancer Treat Rev* **39**, 935-946 (2013).
101. Chetram, M.A. & Hinton, C.V. PTEN regulation of ERK1/2 signaling in cancer. *J Recept Signal Transduct Res* **32**, 190-195 (2012).
102. Bartholomeusz, C.*, et al.* MEK Inhibitor Selumetinib (AZD6244; ARRY-142886) Prevents Lung Metastasis in a Triple-Negative Breast Cancer Xenograft Model. *Molecular Cancer Therapeutics* **14**, 2773-2781 (2015).
103. Giltnane, J.M. & Balko, J.M. Rationale for targeting the Ras/MAPK pathway in triple-negative breast cancer. *Discov Med* **17**, 275-283 (2014).
104. Zhou, Y.*, et al.* Selumetinib suppresses cell proliferation, migration and trigger apoptosis, G1 arrest in triple-negative breast cancer cells. *BMC Cancer* **16**, 818 (2016).
105. De Luca, A., Maiello, M.R., D'Alessio, A., Pergameno, M. & Normanno, N. The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches. *Expert Opin Ther Targets* **16 Suppl 2**, S17-27 (2012).
106. Neuzillet, C.*, et al.* MEK in cancer and cancer therapy. *Pharmacol Ther* **141**, 160-171 (2014).
107. Duncan, J.S.*, et al.* Dynamic reprogramming of the kinome in response to targeted MEK inhibition in triple-negative breast cancer. *Cell* **149**, 307-321 (2012).
108. van der Noord, V.E.*, et al.* An increased cell cycle gene network determines MEK and Akt inhibitor double resistance in triple-negative breast cancer. *Scientific Reports* **9**, 13308 (2019).
109. Bardia, A.*, et al.* Phase Ib Study of Combination Therapy with MEK Inhibitor Binimetinib and Phosphatidylinositol 3-Kinase Inhibitor Buparlisib in Patients with Advanced Solid Tumors with RAS/RAF Alterations. *Oncologist* **25**, e160-e169 (2020).
110. Ramaswamy, B.*, et al.* Abstract LB-216: NCI 9455: Phase II study of trametinib followed by trametinib plus AKT inhibitor,GSK2141795 in patients with advanced triple negative breast cancer. *Cancer Research* **76**, LB-216-LB-216 (2016).
111. Brufsky, A.*, et al.* Abstract P5-21-01: Cobimetinib combined with paclitaxel as first-line treatment for patients with advanced triple-negative breast cancer (COLET study): Primary analysis of cohort I. *Cancer Research* **78**, P5-21-01-P25-21-01 (2018).
112. Brufsky, A.*, et al.* Phase II COLET study: Atezolizumab (A) + cobimetinib (C) + paclitaxel (P)/nab-paclitaxel (nP) as first-line (1L) treatment (tx) for patients (pts) with locally advanced or metastatic triple-negative breast cancer (mTNBC). *Journal of Clinical Oncology* **37**, 1013-1013 (2019).
113. Sun, C.*, et al.* Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers. *Sci Transl Med* **9**(2017).
114. Kurnit, K.C.*, et al.* Abstract CT020: Phase I dose escalation of olaparib (PARP inhibitor) and selumetinib (MEK Inhibitor) combination in solid tumors with Ras pathway alterations. *Cancer Research* **79**, CT020-CT020 (2019).
115. Gross, A.M.*, et al.* SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and

inoperable plexiform neurofibromas (PN). *Journal of Clinical Oncology* **36**, 10503-10503 (2018).
116. Adjei, A.A.*, et al.* Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* **26**, 2139 (2008).
117. Banerji, U.*, et al.* The first-in-human study of the hydrogen sulfate (Hyd-sulfate) capsule of the MEK1/2 inhibitor AZD6244 (ARRY-142886): a phase I open-label multicenter trial in patients with advanced cancer. *Clinical Cancer Research* **16**, 1613-1623 (2010).
118. Leijen, S.*, et al.* A phase I, open-label, randomized crossover study to assess the effect of dosing of the MEK 1/2 inhibitor Selumetinib (AZD6244; ARRY-142866) in the presence and absence of food in patients with advanced solid tumors. *Cancer chemotherapy and pharmacology* **68**, 1619-1628 (2011).
119. LoRusso, P.M.*, et al.* A phase I dose-escalation study of selumetinib in combination with docetaxel or dacarbazine in patients with advanced solid tumors. *BMC cancer* **17**, 173 (2017).
120. Pacey, S.*, et al.* A phase I dose escalation study of the tolerability of the oral VEGFR and EGFR inhibitor vandetanib in combination with the oral MEK1/2 inhibitor selumetinib in solid tumors. *Annals of Oncology* **27**(2016).
121. Ko, A.H.*, et al.* A multicenter, open-label phase II clinical trial of combined MEK plus EGFR inhibition for chemotherapy-refractory advanced pancreatic adenocarcinoma. *Clinical Cancer Research* **22**, 61-68 (2016).
122. Eroglu, Z.*, et al.* A randomised phase II trial of selumetinib vs selumetinib plus temsirolimus for soft-tissue sarcomas. *British journal of cancer* **112**, 1644-1651 (2015).
123. Kirkwood, J.M.*, et al.* Phase II, open-label, randomized trial of the MEK1/2 inhibitor selumetinib as monotherapy versus temozolomide in patients with advanced melanoma. *Clinical Cancer Research* **18**, 555-567 (2012).
124. Catalanotti, F.*, et al.* Phase II trial of MEK inhibitor selumetinib (AZD6244, ARRY-142886) in patients with BRAFV600E/K-mutated melanoma. *Clin Cancer Res* **19**, 2257-2264 (2013).
125. Hayes, D.N.*, et al.* Phase II efficacy and pharmacogenomic study of Selumetinib (AZD6244; ARRY-142886) in iodine-131 refractory papillary thyroid carcinoma with or without follicular elements. *Clin Cancer Res* **18**, 2056-2065 (2012).
126. O'Neil, B.H.*, et al.* Phase II study of the mitogen-activated protein kinase 1/2 inhibitor selumetinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* **29**, 2350-2356 (2011).
127. Bekaii-Saab, T.*, et al.* Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. *J Clin Oncol* **29**, 2357-2363 (2011).
128. Ho, A.L.*, et al.* Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med* **368**, 623-632 (2013).
129. Janne, P.A.*, et al.* SELECT-4: Phase I dose escalation trial of selumetinib (AZD6244, ARRY-142886) in combination with durvalumab (MEDI4736) in patients with advanced solid tumors. (American Society of Clinical Oncology, 2016).
130. Jänne, P.A.*, et al.* Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *The Lancet Oncology* **14**, 38-47 (2013).
131. Hainsworth, J.D.*, et al.* A Phase II, Open-Label, Randomized Study to Assess the Efficacy and Safety of AZD6244 (ARRY-142886) Versus Pemetrexed in Patients with Non-small Cell Lung Cancer Who Have Failed One or Two Prior Chemotherapeutic Regimens. *Journal of Thoracic Oncology* **5**, 1630-1636 (2010).

132. Robert, C.*, et al.* Selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment for BRAF-mutant metastatic melanoma: a phase 2 double-blind randomised study. *Lancet Oncol* **14**, 733-740 (2013).
133. Carter, C.A.*, et al.* Selumetinib with and without erlotinib in KRAS mutant and KRAS wild-type advanced nonsmall-cell lung cancer. *Ann Oncol* **27**, 693-699 (2016).
134. Qiu, Z., Oleinick, N.L. & Zhang, J. ATR/CHK1 inhibitors and cancer therapy. *Radiotherapy and Oncology* **126**, 450-464 (2018).
135. Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61-70 (2012).
136. Sundar, R., Brown, J., Ingles Russo, A. & Yap, T.A. Targeting ATR in cancer medicine. *Current Problems in Cancer* **41**, 302-315 (2017).
137. Mei, L., Zhang, J., He, K. & Zhang, J. Ataxia telangiectasia and Rad3-related inhibitors and cancer therapy: where we stand. *Journal of Hematology & Oncology* **12**, 43 (2019).
138. Ma, C.X.*, et al.* Targeting Chk1 in p53-deficient triple-negative breast cancer is therapeutically beneficial in human-in-mouse tumor models. *The Journal of Clinical Investigation* **122**, 1541-1552 (2012).
139. Vance, S.*, et al.* Selective radiosensitization of p53 mutant pancreatic cancer cells by combined inhibition of Chk1 and PARP1. *Cell Cycle* **10**, 4321-4329 (2011).
140. Cui, Y., Palii, S.S., Innes, C.L. & Paules, R.S. Depletion of ATR selectively sensitizes ATM-deficient human mammary epithelial cells to ionizing radiation and DNA-damaging agents. *Cell Cycle* **13**, 3541-3550 (2014).
141. Al-Subhi, N.*, et al.* Targeting ataxia telangiectasia-mutated- and Rad3-related kinase (ATR) in PTEN-deficient breast cancers for personalized therapy. *Breast cancer research and treatment* **169**, 277-286 (2018).
142. Huntoon, C.J.*, et al.* ATR Inhibition Broadly Sensitizes Ovarian Cancer Cells to Chemotherapy Independent of BRCA Status. *Cancer Research* **73**, 3683-3691 (2013).
143. Morgan, M.A.*, et al.* Mechanism of Radiosensitization by the Chk1/2 Inhibitor AZD7762 Involves Abrogation of the G₂ Checkpoint and Inhibition of Homologous Recombinational DNA Repair. *Cancer Research* **70**, 4972-4981 (2010).
144. Vendetti, F.P.*, et al.* The orally active and bioavailable ATR kinase inhibitor AZD6738 potentiates the anti-tumor effects of cisplatin to resolve ATM-deficient non-small cell lung cancer in vivo. *Oncotarget; Vol 6, No 42* (2015).
145. Dillon, M.T.*, et al.* PATRIOT: A phase I study to assess the tolerability, safety and biological effects of a specific ataxia telangiectasia and Rad3-related (ATR) inhibitor (AZD6738) as a single agent and in combination with palliative radiation therapy in patients with solid tumours. *Clinical and Translational Radiation Oncology* **12**, 16-20 (2018).
146. Dillon, M.*, et al.* 450PD - A phase I study of ATR inhibitor, AZD6738, as monotherapy in advanced solid tumours (PATRIOT part A, B). *Annals of Oncology* **30**, v165-v166 (2019).
147. Bradbury, A., Hall, S., Curtin, N. & Drew, Y. Targeting ATR as Cancer Therapy: A new era for synthetic lethality and synergistic combinations? *Pharmacology & Therapeutics* **207**, 107450 (2020).
148. Peasland, A.*, et al.* Identification and evaluation of a potent novel ATR inhibitor, NU6027, in breast and ovarian cancer cell lines. *British Journal of Cancer* **105**, 372-381 (2011).
149. Tutt, A.*, et al.* VIOLETTE: A randomized phase II study to assess DNA damage response inhibitors in combination with olaparib (Ola) vs Ola monotherapy in patients (pts) with metastatic, triple-negative breast cancer (TNBC) stratified by alterations in homologous recombination repair (HRR)-related genes. *J Clin Oncol* **36**, TPS1116-TPS1111TPS (2018).

150. Lord, C.J. & Ashworth, A. PARP inhibitors: Synthetic lethality in the clinic. *Science* **355**, 1152-1158 (2017).
151. Vinayak, S.*, et al.* Open-label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer. *JAMA Oncology* **5**, 1132-1140 (2019).
152. Domchek, S.M. Reversion Mutations with Clinical Use of PARP Inhibitors: Many Genes, Many Versions. *Cancer Discov* **7**, 937-939 (2017).
153. Bouwman, P. & Jonkers, J. Molecular pathways: how can BRCA-mutated tumors become resistant to PARP inhibitors? *Clin Cancer Res* **20**, 540-547 (2014).
154. Goodall, J.*, et al.* Circulating Cell-Free DNA to Guide Prostate Cancer Treatment with PARP Inhibition. *Cancer Discov* **7**, 1006-1017 (2017).
155. Kondrashova, O.*, et al.* Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. *Cancer Discov* **7**, 984-998 (2017).
156. Vaidyanathan, A.*, et al.* ABCB1 (MDR1) induction defines a common resistance mechanism in paclitaxel- and olaparib-resistant ovarian cancer cells. *Br J Cancer* **115**, 431-441 (2016).
157. Allison Stewart, C.*, et al.* Dynamic variations in epithelial-to-mesenchymal transition (EMT), ATM, and SLFN11 govern response to PARP inhibitors and cisplatin in small cell lung cancer. *Oncotarget* **8**, 28575-28587 (2017).
158. Murai, J.*, et al.* Resistance to PARP inhibitors by SLFN11 inactivation can be overcome by ATR inhibition. *Oncotarget* **7**, 76534-76550 (2016).
159. Boussios, S.*, et al.* Combined Strategies with Poly (ADP-Ribose) Polymerase (PARP) Inhibitors for the Treatment of Ovarian Cancer: A Literature Review. *Diagnostics (Basel)* **9**, 87 (2019).
160. Galluzzi, L., Senovilla, L., Zitvogel, L. & Kroemer, G. The secret ally: immunostimulation by anticancer drugs. *Nat Rev Drug Discov* **11**, 215-233 (2012).
161. Huang, J.*, et al.* The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. *Biochem Biophys Res Commun* **463**, 551-556 (2015).
162. Konstantinopoulos, P.A. Dose-finding combination study of niraparib and pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC) or recurrent platinum-resistant epithelial ovarian cancer (OC) (TOPACIO/Keynote-162). in *ESMO* (2017).
163. Domchek, S.M. An open-label, multitumor, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline
BRCA-mutated (gBRCAm) HER2-negative metastatic breast cancer (MBC). in *San Antonio Breast Cancer Symposium* (San Antonio, TX, USA, 2017).
164. Lee, J.M.*, et al.* Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study. *J Clin Oncol* **35**, 2193-2202 (2017).
165. Kimbung, S.*, et al.* Co-targeting of the PI3K pathway improves the response of BRCA1 deficient breast cancer cells to PARP1 inhibition. *Cancer Letters* **319**, 232-241 (2012).
166. Yi, Y.W., Park, J.S., Kwak, S.J. & Seong, Y.S. Co-treatment with BEZ235 Enhances Sensitivity of BRCA1-negative Breast Cancer Cells to Olaparib. *Anticancer Res* **35**, 3829-3838 (2015).
167. Kim, D., Liu, Y., Oberly, S., Freire, R. & Smolka, M.B. ATR-mediated proteome remodeling is a major determinant of homologous recombination capacity in cancer cells. *Nucleic Acids Research* **46**, 8311-8325 (2018).

168. Konstantinopoulos, P.A.*, et al.* TOPACIO/Keynote-162 (NCT02657889): A phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—Results from ROC cohort. *Journal of Clinical Oncology* **36**, 106-106 (2018).
169. Gruber, J.J.*, et al.* Talazoparib beyond BRCA: A phase II trial of talazoparib monotherapy in BRCA1 and BRCA2 wild-type patients with advanced HER2-negative breast cancer or other solid tumors with a mutation in homologous recombination (HR) pathway genes. *Journal of Clinical Oncology* **37**, 3006-3006 (2019).
170. Puhalla, S.*, et al.* Final results of a phase 1 study of single-agent veliparib (V) in patients (pts) with either BRCA1/2-mutated cancer (BRCA+), platinum-refractory ovarian, or basal-like breast cancer (BRCA-wt). *Journal of Clinical Oncology* **32**, 2570-2570 (2014).
171. Dent, R.A.*, et al.* Phase I trial of the oral PARP inhibitor olaparib in combination with paclitaxel for first- or second-line treatment of patients with metastatic triple-negative breast cancer. *Breast Cancer Res* **15**, R88-R88 (2013).
172. Griguolo, G., Dieci, M.V., Guarneri, V. & Conte, P. Olaparib for the treatment of breast cancer. *Expert Review of Anticancer Therapy* **18**, 519-530 (2018).
173. Cardoso, F.*, et al.* ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast* **23**, 489-502 (2014).
174. Friedlander, M.*, et al.* Practical guidance on the use of olaparib capsules as maintenance therapy for women with BRCA mutations and platinum-sensitive recurrent ovarian cancer. *Asia Pac J Clin Oncol* **12**, 323-331 (2016).
175. Hao, Y., Wolfram, V. & Cook, J. A structured review of health utility measures and elicitation in advanced/metastatic breast cancer. *Clinicoecon Outcomes Res* **8**, 293-303 (2016).
176. Traore, B.M.*, et al.* Evolution of quality of life in patients with breast cancer during the first year of follow-up in Morocco. *BMC Cancer* **18**, 109 (2018).
177. Twelves, C.*, et al.* Health-related quality of life in patients with locally recurrent or metastatic breast cancer treated with etirinotecan pegol versus treatment of physician's choice: Results from the randomised phase III BEACON trial. *Eur J Cancer* **76**, 205-215 (2017).
178. Cortes, J.*, et al.* Health-related quality of life in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial. *Breast Cancer Research and Treatment* **154**, 509-520 (2015).
179. Aaronson NK, A.S., Bergman B. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. European Organization for Research and Treatment of Cancer. *J Natl Cancer Inst* **85**, 365-376 (1993).
180. Efficace, F., Bottomley, A. & van Andel, G. Health related quality of life in prostate carcinoma patients: a systematic review of randomized controlled trials. *Cancer* **97**, 377-388 (2003).
181. Lemieux, J., Goodwin, P.J., Bordeleau, L.J., Lauzier, S. & Théberge, V. Quality-of-Life Measurement in Randomized Clinical Trials in Breast Cancer: An Updated Systematic Review (2001–2009). *JNCI: Journal of the National Cancer Institute* **103**, 178-231 (2011).
182. Sprangers, M.A.*, et al.* The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *Journal of Clinical Oncology* **14**, 2756-2768 (1996).
183. Eisenhauer, E.A.*, et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* **45**, 228-247 (2009).

184. Nishino, M.*, et al.* Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. *Clinical Cancer Research* **19**, 3936-3943 (2013).
185. Aaronson, N.K.*, et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* **85**, 365-376 (1993).
186. Fayers, P., Aaronson, N.K., Bjordal, K. & Sullivan, M. *EORTC QLQ–C30 scoring manual*, (European Organisation for Research and Treatment of Cancer, 1995).
187. Fleming, T.R. One-Sample Multiple Testing Procedure for Phase II Clinical Trials. *Biometrics* **38**, 143-151 (1982).
188. Tsujikawa, T.*, et al.* Quantitative multiplex immunohistochemistry reveals myeloid-inflamed tumor-immune complexity associated with poor prognosis. *Cell reports* **19**, 203-217 (2017).
189. Lin, J.R., Fallahi-Sichani, M., Chen, J.Y. & Sorger, P.K. Cyclic Immunofluorescence (CycIF), A Highly Multiplexed Method for Single-cell Imaging. *Current protocols in chemical biology*, 251-264 (2016).
190. Lin, J.-R., Fallahi-Sichani, M. & Sorger, P.K. Highly multiplexed imaging of single cells using a high-throughput cyclic immunofluorescence method. *Nature communications* **6**, 8390 (2015).
191. Bodenmiller, B. Multiplexed epitope-based tissue imaging for discovery and healthcare applications. *Cell systems* **2**, 225-238 (2016).
192. Dewhirst, M.W. & Secomb, T.W. Transport of drugs from blood vessels to tumour tissue. *Nature Reviews Cancer* **17**, 738 (2017).
193. Swartz, M.A. & Lund, A.W. Lymphatic and interstitial flow in the tumour microenvironment: linking mechanobiology with immunity. *Nature Reviews Cancer* **12**, 210 (2012).
194. Wilson, W.R. & Hay, M.P. Targeting hypoxia in cancer therapy. *Nature Reviews Cancer* **11**, 393 (2011).
195. Fridman, W.H., Pagès, F., Sautès-Fridman, C. & Galon, J. The immune contexture in human tumours: impact on clinical outcome. *Nature Reviews Cancer* **12**, nrc3245 (2012).
196. Yao, S., Fan, L.Y.-N. & Lam, E.W.-F. The FOXO3-FOXM1 axis: A key cancer drug target and a modulator of cancer drug resistance. in *Seminars in cancer biology* (Elsevier, 2017).
197. Baylin, S.B. & Jones, P.A. A decade of exploring the cancer epigenome—biological and translational implications. *Nature Reviews Cancer* **11**, 726 (2011).
198. Tsujikawa, T.*, et al.* Quantitative Multiplex Immunohistochemistry Reveals Myeloid-Inflamed Tumor-Immune Complexity Associated with Poor Prognosis. *Cell Reports* **19**, 203-217 (2017).

15. APPENDICES

APPENDIX A: TREATMENT ARM SELECTION CRITERIA

Results obtained from one or more clinically-validated assays (i.e., laboratory diagnostic test [LDT], or FDA-cleared or approved in vitro diagnostic [IVD] test), under the SMMART Clinical Analytics Platform, using either the pretreatment biopsy or on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days) may be used to determine assignment to Arm 1, Arm 2, Arm 3, or Arm 4. Participants with or without *BRCA* germline mutations are eligible to be assigned to all treatment arms.

A.1. Rules for treatment arm assignment

Participant assignment to a treatment will follow the decision logic presented in **Figure 2**. Initial consideration will be given to those with demonstrable immune activation as described in **A.2.** Participants whose tumor's characteristics match these described criteria will be assigned to Arm 1. Absent these criteria, consideration will next be given to those with one or more alterations to the RAS-MEK pathway as described in **A.3**. If present, these participants will be assigned to Arm 2. If the participant does not meet criteria for Arm 1 or Arm 2, their tumor characteristics will next be assessed for alterations in the PI3K-AKT pathway as described in **A.4**. If such PI3K-AKT alterations are present, then participants will be assigned to Arm 3. If none of the criteria for Arms 1, 2, or 3 are fulfilled, then participants will by default be assigned to Arm 4. Allowable exception(s) to these established rules will be permitted as follows:

1. Nanostring and RNAseq assay thresholds are determined from previously examined TNBC samples. Outliers used for treatment selection criteria in order will be based on outliers:
   a. Levels in the baseline sample
   b. Levels in the treated sample
   c. Change in levels between pre- and on-treatment samples

2. Germline *BRCA* mutation carriers will be allowed entry to all treatment arms; however, , accrual of participants with a germline *BRCA* mutation will be capped at 4 participants per treatment arm, that is:
   a. A two germline *BRCA* participants cap in stage 1
   b. A two germline *BRCA* participants cap in stage 2
   As part of initial consideration for study arm assignment, if Arm 1 has accrued the maximum allowable number of *BRCA* mutants, then participants harboring a BRCA mutation may be considered for assignment to the next treatment arm for which they are eligible (based on established criteria) that has not yet reached its predefined cap. This process of treatment arm assignment may be systematically repeated provided that the participant is eligible for the next available treatment arm and the established *BRCA* mutant cap has not yet been reached. In cases where all treatment arms have reached their allowable quota of BRCA mutants, then study enrollment will be closed to participants harboring a *BRCA* mutation.

3. Participant's with tumors showing androgen receptor (AR) ≥80% by immunohistochemistry are excluded

A.2. Arm 1 (olaparib + durvalumab) Selection Criteria

Participants assigned to this study arm must have one or more of the following criteria:

- Evidence of immune activity based on findings from either the pre-treatment or on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days) showing high tumor mutational burden, defined as ≥10 mutations/megabase [mut/Mb], or
- Presence of basal-like immune-activated (BLIA) molecular sub-type[9] (i.e., RNA) observed on the on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days), or
- Evidence for immune activity based on findings from on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days), defined as:
  - PDL1 ≥ 1% [per IHC]

A.3. Arm 2 (olaparib + selumetinib) Selection Criteria

1. **Genomic aberrations to RAS/RAF/MEK/ERK defined as:**
   - **Findings from either the pre-treatment or on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days) showing genomic alterations in the RAS/MAPK pathway as follows:**
     - Genomic alteration in RAS/MAPK pathway genes[103], including: HRAS, KRAS, MRAS, NRAS, ARAF, BRAF, RAF1, MAP2K1, MAP2K2, MAPK1, MAPK2, MAPK3, ELK1, FOS, ETS1, ETS2, NF1, DUSP4, DUSP6, or
     - RTK (e.g. EGFR, MET), mutations, amplifcations, and/or fusion leading to RAS/MAPK pathway activation

and/or

2. **Nanostring® GeoMx assay (LDT-CLIA):**
   RAS/MAPK pathway activation in aggregate or in single pathway members on Nanostring® based on the pre-treatment, on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days), or changes between biopsies. All values will be assessed relative to reference untreated TNBC biopsy cohort.

A.4. Arm 3 (olaparib + capivasertib) Selection Criteria

1. **Genomic aberrations to PI3K/AKT defined as**
   - **PIK3CA/AKT1/PIK3R1/PTEN-altered status defined as the presence of one or more of the following:**
     - Any Tier I or Tier II mutations in PIK3CA, PIK3R1 or AKT demonstrated to be activating in the literature, COSMIC, ONCOKB or FASMIC
     - *PTEN loss defined by functional mutation as indicated by the literature, COSMIC, ONCOKB or FASMIC, homozygous deletion,*
     - *Loss of PTEN protein expression based on IHC or Nanostring (i.e., absence of PTEN in >90% of tumor cells)*

and/or

2. **Nanostring® GeoMx assay (LDT-CLIA):**
   PI3K/AKT pathway activation in aggregate or in single pathway members on Nanostring® based on the pre-treatment, on-treatment biopsy (i.e., Cycle 1, Day 14 ± 7 days), or changes between biopsies. All values will be assessed relative to reference untreated TNBC biopsy cohort.

A.5. Arm 4 (ceralasertib monotherapy) – Default Arm

Participants whose tumor characteristics do not fulfill the criteria for Arms 1-3 will by default be assigned to Arm 4.

APPENDIX B: SMMART EXPLORATORY RESEARCH ANALYTICS PLATFORM

****Details regarding specimen collection, processing, labeling, and shipping can be found in the SMMART-AMTEC Laboratory Manual****

Multiplex Immunohistochemistry
Comprehensive in situ immune monitoring platform to audit immune composition and functionality with spatial context. Iterative cycles of immunohistochemical staining, scanning, and stripping will be performed on single, unstained slides from patient biospecimen at an OHSU laboratory. A validated antibody panel will be used to characterize tissue sample cell type composition, major immune group composition, as well as lymphoid and myeloid lineage and functional states. Additional antibody panels may be used to perform deeper profiling of specific aspects of the immune contexture.

Cyclic Immunofluorescence
Iterative rounds of multi-color immunofluorescent staining, imaging, and fluorophore quenching may be performed on single, unstained slides from patient biospecimen at an OHSU laboratory. Antibodies will be selected and validated to assess the cellular and extracellular composition, spatial organization, and molecular states (e.g. cell composition, functional protein levels, differentiation state, pathway activity) of tumor cells and their microenvironments.

Reverse Phase Protein Arrays
Bulk characterization of basal protein expression and modification levels for greater than 400 independent analytes will be achieved using Reverse Phase Protein Arrays (RPPA) on patient biospecimen. This assay will be performed by the RPPA Core at MD Anderson. Briefly, frozen tissue will be lysed and protein will be extracted. Diluted lysates will be printed on nitrocellulose-coated slides and probed with validated primary antibodies followed by detection with Biotinylated secondary antibodies. Signal amplification will be achieved using the Vectastain Elite ABC kit from Vector Lab. The slides will be scanned, analyzed, and quantified to generate spot intensity values and estimate relative protein levels.

Electron Microscopy
Electron microscopy (EM) may be performed on tumor tissue to provide visual evidence of response to therapeutic treatment at a resolution that is not obtained via other techniques. Tumor tissue will be fixed, processed, embedded into resin blocks, and imaged at an OHSU core facility. Focused Ion Beam Scanning Electron Microscopy (FIB-SEM) and Serial Block Face Imaging (SBFI) may be utilized to collect high-resolution large-format images and 3D reconstructions of cellular ultrastructure. Correlative light and electron microscopy may be performed and used to provide a full understanding of protein signaling with respect to cellular features.

Experimental Sequencing Analytics
Additional sequencing assays may be performed on tumor tissue and blood samples at an OHSU laboratory or core facility in order to further characterize the genomic, transcriptomic, and/or epigenetic landscape or to explore intratumoral heterogeneity. These assays may include sequencing experiments such as single-cell DNA or RNA sequencing, whole exome sequencing, low-pass whole genome sequencing, and ATAC (Assay for Transposase-Accessible Chromatin) sequencing. Methods for joint profiling may also be used, such as NMT-seq which enables joint profiling of the DNA methylome, chromatin accessibility, and RNA.

Circulating Tumor DNA
DNA from peripheral blood cells and circulating tumor DNA (ctDNA) from plasma may be isolated from patient peripheral blood samples and analyzed using next-generation sequencing at an OHSU laboratory or core facility. Genetic alterations identified in tumor tissue will be compared to those identified in ctDNA from the same time-point in order to estimate the genetic heterogeneity of a patient's disease. ctDNA levels from serial blood samples will be inferred from sequencing results, evaluated for each participant, and correlated with clinical response to therapy.

Circulating Cells
Tumor tissue and circulating hybrid cells (i.e. cells that co-express components of neoplastic cells and immune cell lineages) may be analyzed at an OHSU laboratory or core facility to gain additional insight into tumor evolution. Biopsy tissue and isolated peripheral blood mononuclear cells will be analyzed by assays such as cyclic immunofluorescence to detect protein expression that align with hybrid cell phenotypes and aggressive tumor states (proliferative, developmental, stem cell-like). Longitudinal blood specimen will be analyzed for cell signaling pathway activation to identify treatment response and potential bypass pathway activation. In some collected specimen, hybrid cells will be queried by sequencing assays such as single cell RNA-seq. Resulting data may be correlated with clinical response to therapy.

Experimental Blood Analytics

Other Research Analytics determined to advance the Exploratory Objectives may be performed on peripheral blood collected from research blood draws.. This may include immunophenotyping by methods such as mass cytometry; characterization of cell free DNA, RNA, and proteins by methods such as next-generation sequencing; as well as isolation and characterization of extracellular vesicles by methods such as fluorescence microscopy and next-generation sequencing.

APPENDIX C: PERFORMANCE STATUS

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX D: CONTRACEPTION

Participants of childbearing potential and their partners, who are sexually active, must agree to the use of ONE highly effective forms of contraception and their partner must use a male condom [as listed below]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least:

- 1 month after last dose of olaparib,
- 3 month after last dose of durvalumab
- 1 month after last dose of capivasertib
- 1 month after last dose of ceralasertib

As an alternative to contraception, the participant must totally/truly abstain from any form of sexual intercourse.

Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with an individual that is pregnant or is of childbearing potential for the following periods:

- 3 months after the last dose of olaparib
- 4 months after the last dose of capivasertib
- 6 months after the last dose of ceralasertib

Partners of sperm-producing patients should also use a highly effective form of contraception if they are of childbearing potential. Sperm-producing patients should not donate sperm throughout the period of taking olaparib and for 4 months following the last dose of olaparib, or 4 months following last dose of ceralasertib.

Acceptable Non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month (for participants of childbearing potential) after the last dose of study drug, or for 3 months after last dose *for sperm-producing* participants. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner PLUS condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine device (Provided coils are copper-banded) PLUS male condom.

Acceptable hormonal methods:

- Mini pill PLUS condom: Progesterone-based oral contraceptive pill using desogestrel. Cerazette (Merck Sharp & Dohme) is currently the only highly efficacious progesterone-based pill available.
- Combined pill PLUS condom: Normal and low-dose combined oral pills.
- Injection PLUS condom: Medroxyprogesterone injection (eg, Depo-Provera [Pfizer]).
- Implants PLUS condom: Etonorgestrel-releasing implants (eg, Nexplanon [Merck Sharp & Dohme]).
- Patch PLUS male condom: Norelgestromin/ethinyl estradiol transdermal system (eg, Xulane).
- Intravaginal device (eg, ethinyl estradiol-/etonogestrel-releasing intravaginal devices such as NuvaRing [Merck Sharp & Dohme]) PLUS condom.

- Levonorgestrel-releasing intrauterine system (eg, Mirena [Bayer]) PLUS condom

APPENDIX E: NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.
As published in: The Criteria Committee of the New York Heart Association. (1994).Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.	

APPENDIX F: CANADIAN CARDIOVASCULAR SOCIETY GRADING OF ANGINA PECTORIS

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with st prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair c or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walkin blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in norma
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing on normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, angina syndrome may be present at rest
Reference: L. Campeau (Circulation. 1976; 54: 522-523)	

APPENDIX G: IDENTIFICATION ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW CASES

INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 6.5.10 of this Clinical Study Protocol.

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product (IP).

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

Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

Identification of potential Hy's Law cases

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

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

FOLLOW-UP

Potential Hy's Law criteria not met

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

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

Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 9.7 AE Reporting)
- Notify the AstraZeneca representative

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver eCRF Modules as information becomes available
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and assessment of potential Hy's Law cases

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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

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

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

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

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

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

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

- Report an SAE (report term 'Potential Hy's Law) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients *with liver metastases* who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met.[#]

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative
- A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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 above for Hy's Law criteria not met.

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 above for "Potential Hy's Law criteria met".

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

APPENDIX H: SUMMARY LIST OF CYP1A2, CYP2C8, CYP2C19, CYP3A4, PGP, OATP1B1 AND BCRP SUBSTRATES, INHBITORS AND INDUCERS

The medications described in this appendix are not intended to be an exhaustive list. Refer to FDA Drug Development and Drug Interactions for a more detailed list of inducers, inhibitors, and substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers).

CYP SUBSTRATE(S)

1A2

Amitriptyline
Caffeine
Clomipramine
Clozapine
Cyclobenzaprine
Duloxetine
Estradiol
Fluvoxamine
Haloperidol
Imipramine N-Deme
Mexiletine
Naproxen
Olanzapine
Ondansetron
Phenacetin→Acetaminophen→Napqi
Propranolol
Riluzole
Ropivacaine
Tacrine
Theophylline
Tizanidine
Triamterene
Verapamil
(R)Warfarin
Zileuton
Zolmitriptan

2C8

[Paclitaxel]
Torsemide
Amodiaquine
Cerivastatin
Repaglinide
Sorafinib

2C19

Proton Pump Inhibitors (Ppis):
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

Anti-Epileptics:
Diazepam→Nor
Phenytoin(O)
S-Mephenytoin
Phenobarbitone

Amitriptyline
Carisoprodol
Citalopram
Chloramphenicol
Clomipramine
Chlopidogrel
Cyclophosphamide
Hexobarbital
Imipramine N-Deme
Indomethacin
Labetalol
R-Mephobarbital
Moclobemide
Nelfinavir
Nilutamide
Primidone
Progesterone
Proguanil
Propranolol
Teniposide
R-Warfarin→8-Oh
Voriconazole

3A4

Macrolide Antibiotics:
Clarithromycin
Erythromycin (Not 3a5)
Not Azithromycin
Telithromycin

Anti-Arrhythmics:
Quinidine→3oh (Not 3a5)*

Benzodiazepines:
Alprazolam
Diazepam→3oh
Midazolam
Triazolam

Immune Modulators:
Cyclosporine
Tacrolimus (Fk506)*

Hiv Antivirals:
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Prokinetic:
Cisapride

Antihistamines:
Astemizole*
Chlorpheniramine
Terfenadine*

Calcium Channel Blockers:
Amlodipine
Diltiazem
Felodipine
Lercanidipine
Nifedipine
Nisoldipine
Nitrendipine
Verapamil

Steroid 6beta-Oh:
Estradiol
Hydrocortisone
Progesterone
Testosterone

Miscellaneous:
Alfentanyl*
Aprepitant
Aripiprazole
Boceprevir
Buspirone
Carbamazepine
Cafergot
Caffeine→Tmu
Cilostazol
Cocaine
Codeine-N-Demethylation
Dapsone
Dexamethasone
Dextromethorphan
Docetaxel
Domperidone
Eplerenone
Fentanyl*
Finasteride
Gleevec
Haloperidol
Irinotecan
Laam
Lidocaine
Methadone
Nateglinide
Nevirapine
Ondansetron
Pimozide*
Propranolol
Quetiapine
Quinine
Risperidone
Romidepsin
Not Rosuvastatin
Salmeterol
Sildenafil

CYP SUBSTRATE(S)			
1A2	***2C19***	***3A4***	
		Hmg Coa Reductase Inhibitors: Atorvastatin Cerivastatin Lovastatin Not Pravastatin Not Rosuvastatin Simvastatin	Sirolimus Sorafenib Tamoxifen Taxol Telaprevir Terfenadine Torisel Trazodone Vemurafenib Vincristine Zaleplon Ziprasidone Zolpidem
* Drugs known to be metabolized by CYP3A4 and have a narrow therapeutic index			

CYP2B6 substrates known to have a narrow therapeutic index	
Cyclophosphoamide Ifosfamide Efavirenz Bupropion Propofol Thiotepa Sorafenib Alfentanil Ketamine	Methadone Methoxetamine Nevirapine Propofol Selegiline Sertraline Sorafenib Tamoxifen Valproic Acid

CYP INHIBITORS			
1A2	***2C8***	***2C19***	***3A4***
Fluvoxamine Ciprofloxacin Cimetidine Amiodarone Efavirenz Fluoroquinolones Fluvoxamine Furafylline Interferon Methoxsalen Mibefradil Ticlopidine	Gemfibrozil Trimethoprim Glitazones Montelukast Quercetin	Ppis: Esomeprazole Lansoprazole Omeprazole Pantoprazole Other: Rabeprazole Chloramphenicol Cimetidine Felbamate Fluoxetine Fluvoxamine Indomethacin Ketoconazole Modafinil Oral Contraceptives Oxcarbazepine Probenicid Ticlopidine Topiramate Voriconazole	Hiv Antivirals: Indinavir Nelfinavir Ritonavir Clarithromycin Itraconazole Ketoconazole Nefazodone Saquinavir Telithromycin Aprepitant Erythromycin Fluconazole Grapefruit Juice Verapamil Diltiazem Cimetidine Amiodarone Not Azithromycin Chloramphenicol Boceprevir Ciprofloxacin Delaviridine Diethyldithiocarbamate

			Fluvoxamine Gestodene Imatinib Mibefradil Mifepristone Norfloxacin Norfluoxetine Star Fruit Telaprevir Voriconazole

INDUCERS			
1A2	***2C8***	***2C19***	***3A4***
Broccoli Brussel Sprouts Carbanazepine Char-Grilled Meat Insulin Methylcholanthrene Modafinil Nafcillin Beta-Naphthoflavone Omeprazole Rifampin Tobacco	Rifampin	Carbamazepine Nevirapine Phenobarbital Rifampin Secobarbital St. John's Wort	Hiv Antivirals: Efavirenz Nevirapine Barbiturates Carbamazepine Glucocorticoids Modafinil Oxcarbazepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone

Drugs Known to be Inhibitors of Pgp[a]		**Drugs Known to be Inducers of Pgp[b]**
Amiodarone	Mirabegron	Avasimibe
Azithromycin	Nelfinavir	Carbamazepine
Captopril	Nifedipine	Efavirenz
Carvedilol	Nitrendipine	Genistein
Clarithromycin	Paroxetine	Phenytoin
Conivaptan	Quercetin	Rifampin
Cremophor	Quinidine	St Johns Wort
Curcumin	Ranolazine	
Diltiazem	Rifampin	
Dronedarone	Ritonavir	
Elacridar	Saquinavir/Ritonavir	
Erythromycin	Schisandra Chinensis Extract	
Felodipine	St Johns Wort	
Fluvoxamine	Talinolol	
Ginkgo	Telaprevir	
Indinavir	Telmisartan	
Itraconazole	Ticagrelor	
Ketoconazole	Tipranavir/Ritonavir	
Lapatinib	Tolvaptan	
Lopinavir And Ritonivir	Valspodar (PSC 833)	
Mibefradil	Verapamil	
Milk Thistle		
a. Inhibitors listed for P-gp are those that showed >25% increase in exposure to a P-gp substrate		

Drugs Known to be Inhibitors of Pgp[a]	**Drugs Known to be Inducers of Pgp[b]**
(e.g. digoxin). b. Inducers listed for Pgp are those that showed >20 % decrease in exposure to a P-gp substrate (e.g. digoxin)	

Drugs Known to be Inhibitors of BCRP			**Drugs Known to be inducers of BCRP**
Afatinib	Pantoprazole	Trametinib	Please check individual drugs on a case by case basis
Aripiprazole	Pitavastatin	Trifluoperazine	
Curcumin	Ponatinib	Vismodegib	
Cyclosporine	Quercetin	eltrombopag	
Elacridar	Quizartinib	Atazanavir	
Erlotinib	Rabeprazole	Lopinavir	
Fluvastatin	Regorafenib	Ritonavir	
Fumitremorgin	Rilpivirine	Tipranavir	
Gefitinib	Sulfasalazine	Omeprazole	
Ivermectin	Sunitinib	Estrone	
Lapatinib	Tacrolimus	17b-estradiol	
Nilotinib	Teriflunomide	Imatinib mesylate	
Novobiocin			

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

OATP1B1 substrates		**BCRP substrates**	
Atorvastatin	Methotrexate	Anthracyclines	Mitoxantrone
Fluvastatin	Rifampin	Daunorubicin	nucleoside analogs
Lovastatin	Bosentan	Doxorubicin	prazosin
Pitavastatin	Glyburide	Topotecan	pantoprazole
Pravastatin	Repaglinide	SN-38	topotecan
Rosuvastatin	Valsartan	Irinotecan	rosuvastatin and other
Simvastatin	Olmesartan	Methotrexate	statins
Ezemibe	Atrasentan	Imatinib	teriflunomide
Simvastatin		Irinotecan	chlorothiazide

APPENDIX I: QT PROLONGING MEDICATIONS

The following table describes common medications associated with QT prolongation, but is not intended to be an exhaustive list. Investigators are recommended to consult with pharmacist regarding other medications with QT-prolonging effects.

QT Prolonging Medications

Antimicrobials
Atazanavir
Azithromycin
Bactrim
Ciprofloxacin
Chloroquine
Clarithromycin
Erythromycin
Fluconazole
Fosarnet
Gatifloxacin
Gemifloxacin
Halofantrine
Imipramine
Itraconarole
Ketoconazole
Levofloxacin
Moxifloxacin
Ofloxacin
Pentamidine
Ritonavir
Sparfloxacin
Telithromycin
Voriconazole

Antidepressants
Amitriptyline
Citalopram
Clomipramine
Desipramine
Doxepin
Escitalopram
Fluoxetine
Nortriptyline
Paroxetine
Protriptyline
Sertraline
Trazodone
Trimipramine
Venlafaxine

Antiemetics
Antiemetics
Dolasetron
Domperidone
Droperidol
Granisetron
Odansetron

Anticonvulsants
Felbamate
Fosphenytoin
Phenytoin

Antipsychotics
Chlorpromazine
Clozapine
Haldol
Mesoridazine
Paliperidone
Pimozide
Quetiapine
Risperidone
Sertindole
Thioridazine
Ziprasidone

Antiarrhythmics
Amiodarone
Disopyramide
Dofetilide
Dronedarne
Flecainide
Ibutilide
Nicardipine
Procainanicle
Quinidine
Sotalol

Other Drugs
Alfuzosin
Astemizole
Amantadine
Bepridil
Cisapride
Oiphenhydramine
Eribulin
Famotidine
Fingolimod
Galantamine
Indapamide
Lapatinib
Lithium
Methadone
Moexipril
Nilotinib
Octreotide
Oxytocin
Probucol
Ranolazine
Sunitinib
Tacrolimus
Tamoxifen
Terfenadine
Tizanidine
Vandetanib
Vardenafil