Investigational Drug Substance(s)	Durvalumab (MEDI4736) Olaparib (AZD2281)
Study Number	ESR-19-14545
Version Number	V9
Date	11/25/2022

Durvalumab (MEDI4736) and Olaparib (AZD2281) for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a multicenter pilot study

Investigator / Lead Investigator: Michael Schweizer, MD

Statistician: Roman Gulati, MS

Financial/ Drug Support: AstraZeneca

PROTOCOL SYNOPSIS

Clinical Protocol ESR-19-14545

Study Title: Durvalumab and Olaparib for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a multicenter pilot study
Protocol Number: ESR-19-14545
Clinical Phase: Pilot phase II
Study Duration: 36 months: 12 months recruitment and 24 months individual patient participation **(**6 months active treatment +6 months of follow-up to primary endpoint+12 months follow up to secondary endpoints)
Investigational Product(s) and Reference Therapy: Durvalumab (MEDI4736) solution for infusion after dilution will be supplied in glass vials containing 500 mg durvalumab at a concentration of 50 mg/mL. Olaparib (AZD2281) will be supplied as round or oval green film coated tablets at dosage form 100 mg tablet and150 mg tablet.
Research Hypothesis We hypothesize that high neoantigen load – reflected through loss of function mutations in CDK12 (lfCDK12), mismatch repair deficiency/ microsatellite instability-high (MMRd/MSI-high) or homologous recombination deficiency (HRD) – will result in sensitivity to both immune checkpoint blockade and PARP inhibition.
Objectives: **Primary Objective(s):** • To assess clinical activity of durvalumab and olaparib in men with biochemically recurrent prostate cancer predicted to have a high neoantigen load **Secondary Objective(s)**: • Assess safety of durvalumab monotherapy • Assess safety of durvalumab and olaparib combination therapy • Assess PSA changes in relationship to intervention • Assess quality of life changes **Exploratory Objective(s):** • Assess radiographic progression free survival (rPFS)

- Assess PSA progression free survival (PSA-PFS)
- Assess event free survival (EFS)
- Assess time to start of androgen deprivation therapy (ADT)

Study Assessments and Criteria for Evaluation:

Primary Endpoint(s):

- Undetectable PSA[1,2](post-prostatectomy patients; including those that also received salvage radiation) or PSA <0.5 ng/ml[1] (post-radiation patients) at 12-month timepoint after initiation (cycle 1, day 1) of therapy.

Secondary Endpoint(s):

- Adverse events during durvalumab monotherapy per CTCAE v5.0 guidelines
- Adverse events during durvalumab and olaparib combination therapy per CTCAE v5.0 guidelines
- PSA50 response[1] (at least 50% decline in PSA from baseline at enrollment) at 3- and 6-month timepoints
- Quality of life changes using:
    a. RANDSF-36 two- step 8-scale score (see Appendix IV for algorithm) and
    b. IIEF surveys score in erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction (see Appendix VI for assessment details)

[1] confirmed by repeat measurement at least 2 weeks later
[2] Undetectable PSA defined as PSA <0.1 ng/ml

Exploratory Endpoint(s):

- rPFS, defined as time from enrollment to date of first objective radiographic evidence of metastatic disease (soft tissue or bone lesion) or death; in the absence of an event, PFS will be censored at date of last disease assessment
- PSA-PFS, defined as time from enrollment to PSA progression (increase in PSA by 2 ng/ml and by 25% from baseline/nadir), in the absence of an event, PSA-PFS will be censored at date of last disease assessment and/or visit documenting no next therapy.
- EFS; defined as time from enrollment to initiation of next line of therapy, development of metastatic disease or death; in the absence of an event, EFS is censored at date of last disease assessment and/or visit documenting no next therapy.
- Time to start of ADT; defined as time from enrollment to initiation of ADT; in the absence of an event, the endpoint is censored at date of last visit documenting no ADT initiation

Correlative Objectives and Endpoints:

1. **Objective**: identify favorable tumor microenvironment associated with response to durvalumab and olaparib
   Endpoint: CD8, CD4, FOXB3, PDL1 by IHC with quantitative output on archival prostate cancer tissue
2. **Objective**: identify genetic characteristics associated with response to durvalumab and olaparib

Endpoint: number of somatic mutations, mutational signature, and DNA variants on whole exome or targeted gene sequencing of archival prostate cancer tissue

3. **Objective**: to evaluate tumor clonal evolution
   Endpoint: next generation sequencing of peripheral blood cell-free circulating tumor DNA (ctDNA) to evaluate mutational burden, and DNA variants in ctDNA at enrollment, at 6 months and at the time of progression
4. **Objective**: evaluate systemic immune response at 3 and 6 months and at the time of progression
   Endpoint: on peripheral blood measure cytokines using Cytokine Human Magnetic 35-Plex Panel for the Luminex™ platform; T-cells population using flow cytometry and T-cell receptor sequencing.

Study Design: This is a multicenter pilot phase 2, prospective, single arm, three cohort, open label trial that will investigate the clinical activity of durvalumab and olaparib in men with biochemically recurrent (BCR) prostate cancer predicted to have a high neoantigen load inferred by the presence of either loss of function mutations in CDK12 (lfCDK12; Cohort A), MMRd/MSI-high (Cohort B), or loss of function mutations in homologous recombination genes (i.e. HRD; Cohort C). Patients in cohort A and B will receive durvalumab monotherapy for 3 months followed by durvalumab plus olaparib for an additional 3 months. Patients in Cohort C will receive 6 months of durvalumab and olaparib combination therapy. Patients will be seen by research and oncology teams every 4 weeks while receiving durvalumab, and then every 3 months with PSA testing until completion of 24 months. Radiographic assessment (i.e., CT chest, abdomen and pelvis and bone scan) will be performed upon enrollment (within 6 weeks before study therapy start date) and then obtained as prompted by signs and symptoms of metastatic disease and/or at the time of PSA progression (increase in PSA by 2 ng/ml and by 25% from baseline). Upon completion study visits (24 months from starting durvalumab) patients will continue to be followed as per standard of care. Clinical data after 24 months will be extracted from the clinical chart by the study team, as permitted by the patient. Patient will be followed passively through following clinical chart data up to 5 years total.

Number of Centers: 2

Performance Sites:

Coordinating Center: University of Washington / Fred Hutch Cancer Center	**Lead Investigator: Michael Schweizer, MD**
Participating Site: Oregon Health and Science University (OHSU)	**Investigator: Alexandra Sokolova, MD**

Number of Patients: 30

Study Population: The study aims to enroll patients with BCR prostate cancer with one of the following biomarkers: lfCDK12, MMRd/MSI-high, or HRD.

Inclusion Criteria:

- Histologic confirmation of adenocarcinoma of the prostate
- The patient must have received definitive local therapy for prostate cancer, consisting of either radiation therapy and/or prostatectomy (salvage or adjuvant radiation post-prostatectomy is not exclusionary).
- PSA must be ≥2 ng/ml if received only prior definitive radiation (no PSA threshold required if prior prostatectomy was performed) with a PSA doubling time (PSADT) ≤10 months:
    - PSADT calculation must include all recorded PSA values >0.1 ng/ml over the past 6 months prior to randomization, with a minimum of 3 values spaced at least 2 weeks apart, with each included value preferably measured at the same laboratory. PSA values obtained prior to localized therapy will be excluded.
    - The calculation of PSADT is based on the natural log of PSA.
    - The actual calculation of the PSADT can be obtained from the following online calculator: http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx
- Prior salvage radiation or not a candidate for localized salvage radiation due to subject preference or clinical assessment based upon disease characteristics and/or subject co-morbidities.
- Prior hormonal therapy (e.g. androgen deprivation therapy, oral AR-signaling inhibitors) is allowed, provided this was stopped ≥ 6 months prior to starting treatment per protocol, testosterone is ≥150 ng/dl and patient did not demonstrate evidence of castration-resistance while on hormonal therapy (i.e. PSA was not rising on treatment).
- No evidence of metastatic disease on imaging by whole body bone scan and CT or MRI of the chest/abdomen/pelvis within 6 weeks before study therapy start day. PSMA PET or Fluciclovine scan within 6 weeks of start day may substitute other imaging studies.
    - Patients with oligometastatic disease (i.e., ≤3 sites) detectable on advanced imaging only (e.g., PSMA or Fluciclovine PET) are eligible. Note: Prior site directed radiation is allowed; however, PSA must be rising following radiation as indicated above.
    - Abdominal or pelvic lymph nodes measuring ≤2 cm in short axis are allowed.

- Biomarker positive:
  - Biallelic *CDK12* inactivating mutations as documented using a clinical grade sequencing assay performed in a Clinical Laboratory Improvement Amendments (CLIA) or College of American Pathologists (CAP) certified laboratory

  or
  - MMRd/MSI-high as documented using a clinical grade sequencing assay performed in a CLIA/CAP certified laboratory

  or
  - Loss of function mutations in homologous recombination genes (i.e., homologous recombination deficiency; HRD) as documented using a clinical grade sequencing assay performed in a CLIA/CAP certified laboratory. Homologous recombination genes include, but not limited to *BRCA1, BRCA2, ATM, CHEK2, PALB2, RAD51D, NBN, GEN1, RAD51C, MRE11A, BRIP11A, FAM175A.*

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

- Age ≥ 18 years at time of study entry.

- Eastern Cooperative Oncology Group (ECOG) performance status of ≤1

- Adequate normal organ and marrow function as defined below measured within 28 days prior to administration of study treatment as defined below:

  - Hemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days

  - Absolute neutrophil count (ANC) be ≥1.5 x 10^9/L

  - Platelet count ≥100 x 10^9/L

  - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

  - AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN

  - Patient must have creatinine clearance (CL) ≥51 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

- Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
- Patients must have a life expectancy ≥ 16 weeks.
- Body weight >30 kg
- Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (Table10 for acceptable methods]) if they are of childbearing potential.

Exclusion Criteria:

- Prior chemotherapy for prostate cancer, unless done in the neoadjuvant setting, and if the last dose was >6 months prior to enrolment
- Any prior treatment with a PD1 or PD-L1 inhibitor, including durvalumab
- Any prior treatment with PARP inhibitor, including olaparib
- History of another primary malignancy except for
    - Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of durvalumab and of low potential risk for recurrence
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease
- History of leptomeningeal carcinomatosis
- Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the treating physician (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >470 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.
- Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or olaparib may be included only after consultation with the Study Physician.

- Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

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

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

- Immunocompromised patients, e.g., patients with uncontrolled human immunodeficiency virus (HIV). HIV+ patients will be allowed on the study if on HAART and disease is controlled: CD4≥350cell/mcl, undetectable viral load, and no PPX antibiotics.

  Note: HIV screening is not required to be eligible for this study.

- Active infection including **tuberculosis** (TB testing only performed if deemed necessary per standard clinical practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C.** Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

- 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:

  - Patients with vitiligo or alopecia

  - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the Investigator
- Patients with celiac disease controlled by diet alone

- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
  - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
  - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
- Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: Patients, if enrolled, should not receive live vaccine whilst receiving durvalumab and up to 30 days after the last dose of durvalumab.
- Patients receiving any chemotherapy, immunotherapy, biologic, radiotherapy or hormonal therapy for cancer treatment concurrently or within 3 weeks of study treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting *study treatment* is 2 weeks.
- Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting *study treatment* is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
- Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

- Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
- Participation in another clinical study with an investigational product administered in the last 3 months
- Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) or supportive care, while on the clinical study or during the follow-up period of this interventional study
- Patients with a known hypersensitivity to olaparib or durvalumab or any of the excipients of the product.
- Involvement in the planning and/or conduct of the study

Investigational Product(s), Dose and Mode of Administration:

Patients will receive 1500 mg durvalumab via IV infusion Q4W for 24 weeks (up to 6 doses/cycles) with the last administration on week 20 (N.B. If a patient's weight falls to 30kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between the treating physician and Investigator, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W).

Patients in Cohorts A and B will receive Olaparib 300 mg Q12 starting week 13 and with last dose administered on week 26. Patients in Cohort C will receive Olaparib 300 mg Q12 weeks starting concurrently with durvalumab.

Study treatment will be discontinued if there is evidence of metastatic disease on conventional imaging or there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Statistical Methods and Data Analysis:

Within each cohort, a response rate of 30% or greater (response as defined in Section 6.1.5) would be a meaningful indicator of clinical activity and a response rate below 5% would be considered not clinically meaningful. The sample size was selected based on precision of a two-sided 90% confidence interval (CI) for the response rate; the exact binomial 90% CIs for 0 to 5 responses are tabulated below. Observing 3 or more responses among 10 patients would provide a two-sided 90% CI with lower confidence limit above 5%.

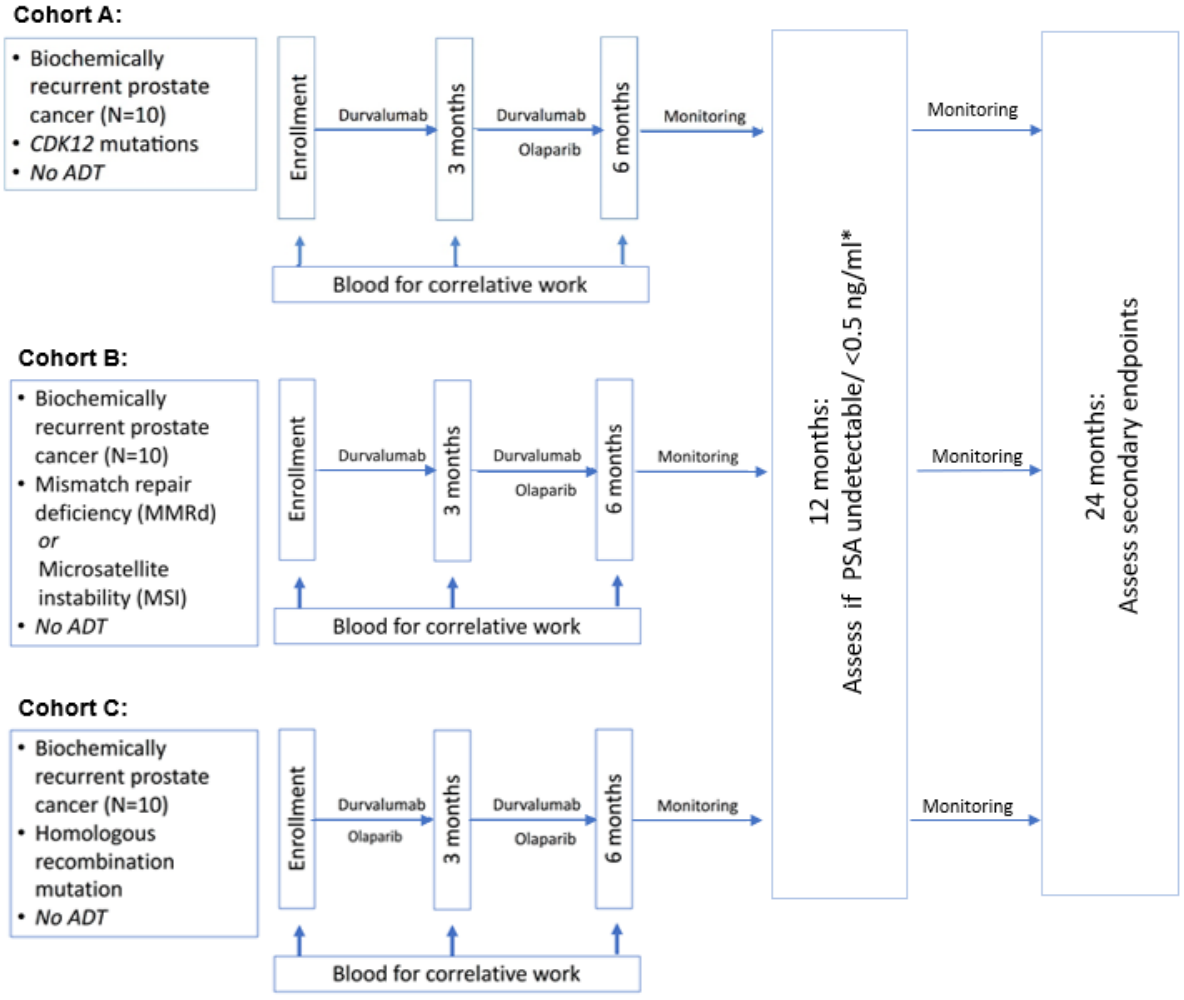
N. responses[3]	0	1	2	3	4	5
Response[3] rate	0%	10%	20%	30%	40%	50%

90% CI	0-25.9	0.5-39.4	3.7-50.7	8.7-60.7	15.0-69.7	22.2-77.8

[3]response defined as meeting primary endpoint (see definition above and in Section 6.1.5)

Sample Size Determination: For this multicenter pilot study, ten patients will be enrolled in each cohort (total 30). We anticipate identifying the majority of the study cohort (N≈20) prior to screening; however, we are expecting to screen 50 patients without prior clinical sequencing to identify the remaining cohort (N≈10).

Study Schema:



*Undetectable PSA for post-prostatectomy patients (including those that also received salvage radiation) or PSA <0.5 ng/ml for post-radiation patients

TABLE OF CONTENTS

PAGE

Contents

LIST OF TABLES:

ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADT	Androgen deprivation therapy
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APC	Antigen-presenting cells
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCR	Biochemically recurrent prostate cancer
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CDC	Complement-dependent cytotoxicity
CFR	U.S. Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CLIA	Clinical laboratory improvement amendment
C_{max}	Peak concentration
$C_{max,ss}$	Peak concentration at steady state
C_{min}	Trough concentration
$C_{min,ss}$	Trough concentration at steady state
CNS	Central nervous system
CR	Complete response
CRPC	Castration resistance prostate cancer
CT	Computed tomography
CTCAE v.50	Common Terminology Criteria for Adverse Events
ctDNA	Cell-free circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4

Abbreviation or special term	**Explanation**
DC	Disease control
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ds-DNA	Double strand DNA
E2A	Clinical safety data management: definitions and standards for expedited reporting
E6	Good clinical practice: consolidated guidance
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status
EDTA	Disodium edetate dihydrate
EFS	Event free survival
Fc	Fragment crystallizable
FFPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
FTIH	First-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCl	Hydrochloride
HCV	Hepatitis C virus
HDL	High Dense Lipoprotein
HIV	Human immunodeficiency virus
HR	Homologous recombination
HRD	Homologous recombination deficient (loss of function mutation in homologous recombination gene)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
iCPD	confirmed progressive disease by iRECIST
IEC	Independent Ethics Committee
IFN	Interferon
IGF	Insulin-like growth factor
IgG1	Immunoglobulin G1
IgG2	Immunoglobulin G2
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry

Abbreviation or special term	**Explanation**
IIEF	International index of erectile function
IL	Interleukin
imAE	Immune-mediated adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
LC/MS/MS	Liquid chromatography/tandem mass spectrometry
LDL	Low Dense Lipoprotein
lfCDK12	Loss of function CDK12 mutation
LL	Local laboratories
MAb	Monoclonal antibody
mCRPC	Metastatic castration resistance prostate cancer
MDS	Myelodysplastic syndrome
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MMR	Mismatch repair
MMRd	Mismatch repair deficiency
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next generation sequencing
NHEJ	Non-homologous end-joining pathway
NIH	National Institution of Health
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PCa	Prostate cancer
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression free survival

Abbreviation or special term	**Explanation**
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PSA	Prostate specific antigen
PSA50	Decrease of PSA by ⩾ 50% from baseline
PSADT	PSA doubling time
PT	Prothrombin time
PVC	Polyvinyl chloride
Q12W	Every 12 weeks
Q2W	Every 2 weeks
Q3M	Every 3 months
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QC	Quality control
QOL	Quality of life
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RANDSF-36	RAND 36-Item Short Form QOL Survey
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse events
SD	Stable disease
SID	Subject identification
SoAs	Schedule of Assessments
SOCS3	Suppressor of cytokine signaling 3
sPD-L1	Soluble programmed cell death ligand 1
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half life
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
T_{max}	Time to peak concentration

Abbreviation or special term	**Explanation**
$T_{max,ss}$	Time to peak concentration at steady state
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USA	United States of America
UW	University of Washington
WBC	White blood cell
WFI	Water for injection
WHO	World Health Organization

1. INTRODUCTION

1.1 BIOCHEMICALLY RELAPSED PROSTATE CANCER

Prostate cancer is the most common non-cutaneous malignancy affecting American men and is expected to result in nearly 30,000 deaths in the U.S. in 2018.(1) This year, an estimated 174,650 men in the United States will be diagnosed with prostate cancer, of which about two-thirds undergo radical prostatectomy or definitive radiation therapy (RT). Approximately 25%-35% of patients treated with definitive surgical or radiation therapy for localized adenocarcinoma of the prostate will develop biochemically recurrent prostate cancer (BCR), characterized by elevated prostate specific antigen (PSA) without presence of overt metastatic disease.(2,3) Definition of BCR differs depending on what treatment patients received for local disease. For patients who underwent radical prostatectomy BCR is defined by American Urological Association as a serum PSA ≥0.2 ng/mL, which is confirmed by a second determination with a PSA ≥0.2 ng/mL. Phoenix criteria is used to define BCR in patients who underwent definitive radiation therapy without prostatectomy: a PSA rise of 2 ng/mL or more above the nadir PSA. An estimated 40,000 - 50,000 men in the U.S develop BCR each year, yet the treatment of men in this disease state is far from standardized. The optimal time to initiate treatment and the choice of specific therapy for such patients remains controversial and highly variable in clinical practice. This may be due to several potential reasons, including 1) a lack of prospective randomized trial data demonstrating an overall survival advantage for one particular therapeutic approach and 2) a biologically heterogeneous population with variable natural disease course. The kinetics of PSA change over time has emerged as an important independent prognostic factor for patients with BCR, both with respect to time to development of metastases as well as the risk of prostate cancer-specific mortality. In a cohort study of 8,669 men treated with localized therapy, of the 1,451 men with PSA recurrence, a PSA doubling time (PSADT) less than 3 months was associated with an approximately 50% chance of prostate-cancer specific mortality at 5 years; in contrast, those with a PSADT greater than 12 months had less than 10% prostate cancer-specific mortality during the same time interval.(4)

1.2 TREATMENT OPTIONS IN BCR PROSTATE CANCER PATIENTS

Guideline recommendations from the National Comprehensive Cancer Network (NCCN), for management of BCR include androgen deprivation therapy (ADT) or observation. Currently, there are no clear guidelines about the best time to start therapy for BCR patients. NCCN guidelines suggest considering observation in men with prolonged PSADT (>12 months) and those who are older. Earlier ADT is suggested in men with shorter PSADT and otherwise long-life expectancy, though the definition of earlier and late ADT is controversial and are not defined in guidelines. Since the benefit of early ADT is not clear and ADT can increase morbidity and negatively impact quality of life (Section 1.3), treatment is recommended to be individualized until further studies are done. (5) BCR patients who choose to proceed with ADT can be treated with intermittent ADT or continuous ADT as a randomized clinical trial with 1386 enrolled patients showed that intermittent ADT is not inferior to continuous ADT in BCR patients.(6) In this trial, BCR patients (defined by PSA> 3 ng/ml) were randomized to continuous ADT or to intermittent ADT (8-month cycles of ADT with nontreatment periods determined according to the PSA level). For the patients on intermittent ADT, if their PSA was >4ng/ml; rising during an ADT treatment cycle; or PSA>10 ng/ml less than 2 months after finishing 8-month ADT treatment cycle, they were switched to continuous ADT therapy. Intention to treat analysis showed that median overall survival was 8.8 years in the intermittent-

therapy group versus 9.1 years in the continuous-therapy group (hazard ratio for death, 1.02; 95% confidence interval, 0.86 to 1.21).(6)) Quality of life (QOL) assessment in this trial showed better scores with intermittent ADT for hot flashes, desire for sexual activity, and urinary symptoms. Based on this data, intermittent ADT can be considered over continuous ADT in BCR if the decision is to start therapy, though patients often end up on a long-term ADT therapy.

1.3 ADT EFFECTS ON QUALITY OF LIFE AND METABOLISM

Patients that undergo localized prostate cancer therapy, prostatectomy or radiation therapy, suffer from sexual, urinary and bowel morbidities(7). ADT worsens these morbidities and further decreases quality of life (QOL) in prostate cancer patients. A population study assessing QOL in prostate cancer patients was conducted in the UK. QOL surveys were completed by 35823 men with all stages of prostate cancer, 19599 (63.8%) had stage I or II. Compared with men who did not receive ADT, more men who received the therapy reported moderate to large problems with hot flushes (30·7% [95% CI 29·8–31·6] vs 5·4% [5·0–5·8]), low energy (29·4% [95% CI 28·6–30·3] vs 14·7% [14·2–15·3]), and weight gain (22·5%, 21·7–23·3) vs 6·9% [6·5–7·3]). EPIC-26 score was used to assess sexual function (100 - the best, 0 - the worst) and showed that men on ADT had worse sexual function (score 15.3, CI 14.6-16.1) compared to men on active surveillance (score 44.6 CI 43.6-45.7) or men who had surgery alone (score 22.1 CI 21.5-22.6). Patients who had external beam radiation (EBRT) alone had sexual function score of 25.6 (CI 24.5-26.7) compared to score 19.1 (18.5-19.6) in patients who had EBRT and ADT. Aside from negative affect on quality of life, ADT also impacts metabolism. ADT causes weight gain: loss of muscle mass and increase of fat mass.(8) ADT causes elevated lipid profile, insulin resistance, increasing risk of diabetes and cardiovascular disease. (8) ADT has also been associated with cognitive impairment (9), osteoporosis and an increased risk of fractures(10). Despite these negative effects ADT remains the main backbone therapy for prostate cancer, as it is very effective for disease control, but strategies to postpone the start of ADT can help to reduce morbidity and improve quality of life in prostate cancer patients.

1.4 CHECKPOINT INHIBITORS IN CANCER TREATMENT

Traditionally, prostate cancer has been treated with a *one size fits all* therapeutic approaches, utilizing hormonal therapies, chemotherapies, and radiopharmaceuticals. While advances in systemic therapy have resulted in improved cancer outcomes over the past decades, we are now entering an era of *precision oncology* in which our understanding of cancer biology and genomics will allow us to select a therapy with the greatest likelihood of benefiting an individual. Indeed, proof of principle for this concept is evidenced by pembrolizumab's recent approval by the FDA for all advanced solid tumor patients with mismatch repair (MMR) deficiency (MMRd) or microsatellite instability (MSI) – representing the first tumor-agnostic approval by the Agency (11–13). About 5% of castration-resistant prostate cancer (CRPC) cases have been shown to be MMRd/MSI-high and would thus qualify for treatment with pembrolizumab. (14)

While immunotherapeutics have demonstrated impressive activity in a range of malignancies, they are not effective for all patients and strategies to identify patients most likely to benefit from these agents are needed. The major role of the adaptive immune system is to recognize and destroy cells displaying foreign antigens, including tumor cells. A clinically relevant mechanism by which cancers are able to escape T-cell mediated destruction is through stimulating the programmed death 1 (PD1) pathway – a negative feedback system that represses Th1 cytotoxic immune responses.(15) Recent advances have shown that blocking this

pathway with antibodies directed towards PD1 or its ligand (PDL1) can produce remarkable clinical responses in some cancers.(16–21)This immune-recognition is predicated, however, on the presence of antigens that are recognized as foreign (i.e. tumor neoantigens). Not surprisingly, a high burden of tumor neoantigens – as reflected by a high somatic mutational load – has been shown to correspond with the response to immune checkpoint blockade (e.g. anti-CTLA4, anti-PD1, anti-PDL1). (13,22–24)

Based on the hypothesis that hypermutation would predispose to anti-PD1 therapy, a phase II study testing pembrolizumab (anti-PD1 therapy) in patients with metastatic carcinoma with and without MMRd (i.e. MSI-high and MSI-low, respectively) was launched.(13)This study demonstrated that 40% of hypermutated (i.e. MSI-high) colorectal cancer patients had an immune-related objective response (irOR) compared to 0% of MSI-low patients. Similarly, pembrolizumab was associated with a 50% response rate in hypermutated non-colorectal gastrointestinal malignancies – supporting the hypothesis that mutational load may predict for response to immune checkpoint blockade in a range of malignancies.(20) An expansion cohort testing pembrolizumab across 12 different MSI-high and/or MMRd cancers confirmed a response rate of ~50% for this group – leading to pembrolizumab's approval in this molecularly defined group of patients.(11,20) However, some non-hypermutated tumors still respond to immune checkpoint blockade, which would indicate that neoantigens are likely being generated in the absence of MMRd.

1.5 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; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). 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 .(25) *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism.(25) Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor 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 4.2 and Section 16.5.1. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.6 CDK12 DEFICIENCY AND NEOANTIGEN BURDEN

Recent work conducted through the Stand Up 2 Cancer-Prostate Cancer Foundation (SU2C-PCF) Prostate Dream Team has found that *CDK12* loss of function mutations lead to increased gene fusions, with a distinct mutational signature compared to cases with inactivating mutations in homologous recombination (e.g. *BRCA1/2*, *ATM*) or MMR genes. Interestingly, *CDK12*-mutant cases are associated with elevated neoantigen burden ensuing from fusion-induced chimeric open reading frames. Their immune phenotype is characterized by increased tumor T-cell infiltration, high levels of neoantigens, and T-cell clonal expansion. Clinically, we have observed responses to pembrolizumab in 4/6 men with MSI-low, castration-resistant prostate cancer (CRPC) and *CDK12* inactivation, which is double the response rate in unselected CRPC patients.(26)

The incidence of *CDK12* mutations appears to be enriched in CRPC compared to unselected primary prostate cancer cases (6.9% *vs.* 1.2%). However, the incidence of *CDK12* mutations in primary prostate specimens from men who subsequently developed CPRC is comparable to what is observed in metastatic tissue from men with CPRC – indicating that *CDK12* mutations are a likely early (i.e. truncal) event.(27)

1.7 DNA REPAIR AND HOMOLOGOUS RECOMBINATION DEFICIENCY

There are several DNA repair pathways. The main repair mechanisms for double-stranded DNA (dsDNA) damage repair are the homologous recombination (HR) pathway and non-homologous end-joining (NHEJ) pathways. NHEJ joins then ends of the damaged DNA without repairing lost DNA information, leading to loss on DNA code and eventually cell apoptosis. The only pathway that repairs dsDNA damage without loss of DNA code is the HR pathway. If a patient has a mutation in a HR pathway gene (e.g. *BRCA1/2, ATM, CHEK2*, etc.), agents that induce dsDNA damage can lead to replication fork collapse and chromatid breaks persist, leading a cell down a pathway toward apoptosis.(28–30)

In spite of the higher neoantigen burden associated with HR deficient (HRD) prostate cancer, single agent checkpoint inhibitors do not appear to be very effective in these patients. The KEYNOTE-199 study reported a PSA response rate of only 12% in mCRPC patients post taxane-based chemotherapy with *ATM* or *BRCA1/2* mutations, with a similar PSA response rate of 10% observed in the HRD unselected group.(39) Response rates to combined CTLA4/PD1-pathway blockade (ipilimumab + nivolumab) were reported to be higher in the CheckMate 650 trial, with responses potentially enriched in those with HRD; however, definitive conclusions about HRD status as a biomarker for response to dual checkpoint blockade are not possible given that few patients with HRD were enrolled to this trial (N=7). It is also worth noting that ipilimumab + nivolumab was associated with considerable toxicity, with >40% of patients experiencing a treatment-related grade 3-5 adverse event and 4 (4%) patients experiencing a treatment-related death.(40)

1.8 OLAPARIB BACKGROUND/NON-CLINICAL AND CLINICAL EXPERIENCE

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (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. Treating physician and Investigator should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB).

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Over 20% of CRPC patients harbor biallelic loss of an HR pathway gene.(41) In addition, more recent studies from our group have demonstrated that in men with metastatic prostate cancer, there is a high incidence (>10%) of deleterious germline alteration in HR genes.(42) This data provides a strong rationale for a precision oncology approach to treating advanced prostate cancer with drugs that impair DNA damage repair (e.g. PARP inhibitors). Proof of concept for this approach is derived from the TOPARP Trial, in which the PARP inhibitor olaparib was found to associate with a response rate of 88% in men with homozygous deletions, deleterious mutations, or both in DDR genes (e.g. *BRCA1/2*, *ATM*, Fanconi's anemia genes, and *CHEK2*).(43) On this basis, larger randomized studies have been launched to further evaluate PAPR inhibitors in men with CRPC.

Olaparib increases genomic instability and may sensitize to checkpoint inhibitors through increasing mutational burden or leading to STING pathway activation. Preliminary findings from a Phase I/II trial testing durvalumab (anti-PDL1) in combination with olaparib, an inhibitor of poly(ADP-ribose) polymerase (PARPi), reported that 9 of 17 (53%) patients had a radiographic and/or PSA response, the majority of patients that responded to combinatorial therapy had inactivating mutations in HR genes.(44) Cohort A of the KEYNOTE-365 study tested pembrolizumab in combination with olaparib in unselected mCRPC patients and reported that ~1/3 of patients had a radiographic response per PCWG3-modified RECIST criteria. Overall, incidence of immune-mediated adverse events (AEs) in KEYNOTE-365 was consistent with studies testing pembrolizumab monotherapy. Based on these promising results, larger studies testing immune checkpoint inhibition plus PARP inhibitors are currently planned.

2. RESEARCH HYPOTHESIS

ADT or observation are currently standard of care for BCR patients. Given that ADT can negatively impact quality of life (QOL) and often results in clinically significant morbidity (e.g. metabolic derangements, osteoporosis, cognitive impairment), new therapeutic strategies for BCR patients that avoid/postpone ADT are needed. Based on the aforementioned data, we *hypothesize that BCR prostate cancer patients with a high neoantigen burden – as inferred by loss of function mutations in CDK12, MMRd/MSI-high or HRD in archival tumor tissue – will be sensitive to durvalumab plus olaparib when given in the absence of ADT.*

3. RATIONALE FOR CONDUCTING THIS STUDY

3.1 RATIONALE FOR PSA AS SURROGATE ENDPOINT IN BCR

Analysis of University of Washington Caisis database was done to assess the association of undetectable PSA with development of metastasis, prostate cancer-specific survival, and overall survival. (48) In this study, 93 patients after radical prostatectomy who developed BCR (defined as PSA ≥0.2 ng/mL) and received 6-12 months of ADT were included in the analysis. Retrospective analysis showed that 23/93 (25%; 95%CI 16-35%; $p < 0.001$) patients had undetectable PSA at 12 months and 14/93 (15%; 95%CI 9-24%; $p < 0.001$) at 24 months after ending ADT. Detectable PSA at 12 months was associated with increased risk of metastasis ($p = 0.006$), prostate cancer-specific death ($p = 0.028$), and death from any cause ($p = 0.065$). Though this study is limited by retrospective nature, it suggests that undetectable PSA at 12 months is associated with longer prostate cancer-specific survival and lower risk of metastatic disease. Further, given PSA level and rate of increase regularly informs decision to start ADT and ADT is associated with significant morbidity (Section 1.3), achieving an undetectable PSA and delaying time to ADT can be beneficial for patients. Therefore, in this protocol, we chose undetectable PSA at 12 months as our primary endpoint for patients previously treated with radical prostatectomy, including those that also went on to receive salvage radiation.

In contrast to post-prostatectomy, following definitive radiation, prostate cancer patients still have viable prostate tissue that can produce PSA. As such, Critz, et al. conducted work to define the PSA nadir post-radiotherapy associated with long-term disease-free survival. This study concluded that a PSA nadir of 0.5 ng/mL or less was associated with best outcomes. Men with a PSA nadir of ≤0.5 ng/mL were found to have a 5- and 10-year disease-free survival rate of 93% and 83%, respectively, as compared with a 5-year disease-free survival rate of 26% for those achieving a nadir of 0.6 to 1.0 ng/mL ($P = 0.0001$). All men with a nadir greater than 1.0 ng/mL ultimately failed treatment.(49) Based on this data we chose PSA < 0.5 ng/ml as primary endpoint for BCR patients who underwent definitive radiation therapy without prostatectomy.

3.2 DURVALUMAB DOSE RATIONALE

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 17 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab.

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (see Investigator's Brochure for details). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

3.2.1 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.(50–53) Wang and colleagues 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.(52) 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.(50)

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given 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.

3.3 OLAPARIB DOSE RATIONALE

The dose of olaparib used in this study is 300 mg twice daily which is the currently approved dose.

3.4 COMBINATION OF OLAPARIB AND DURVALUMAB RATIONALE

Olaparib increases genomic instability, which may sensitize tumors to immune checkpoint blockade by increasing mutational burden or activating pro-inflammatory pathways (e.g. STING pathway). As cited above, preliminary findings from a Phase I/II trial testing durvalumab in combination with olaparib reported 9 of 17 (53%) patients had a radiographic and/or PSA response. In addition, the KEYNOTE-365 study also reported a favorable response rate to combination pembrolizumab plus olaparib. Both trials reported an acceptable safety profile. This data supports the use of durvalumab plus olaparib as a well-tolerated, highly effective immunotherapy regimen. We anticipate that this combinatorial regimen will be associated with durable PSA suppression in men with BCR prostate cancer and a high neoantigen burden.(44)(54,54,55)

Given that we expect some BCR prostate cancer patients with lfCDK12 (Cohort A) and MMRd/MSI-high (Cohort B) may respond well to durvalumab alone, we are planning to treat these patients with a 3-month durvalumab lead-in prior to adding olaparib to their regimen. This will allow us to determine the PSA response rate and assess the impact on circulating immune markers following anti-PDL1 monotherapy in Cohorts A and B. Because prostate cancer patients with HRD have not demonstrated high response rates to immune checkpoint inhibitor monotherapy, we will plan to treat these patients (Cohort C) with durvalumab plus olaparib for the entire study treatment period.

Safety

In the aforementioned Phase I/II study testing durvalumab plus olaparib trial (44) the most common treatment-related grade 3 or 4 adverse events were anemia (4/17; 24%), lymphopenia (2/17; 12%), infection (2/17; 12%), and nausea (2/17; 12%). Four patients had immune-related adverse events (imAEs) of any grade, including 2 with acute onset unilateral hearing loss, one with optic neuritis, and one who developed remitting seronegative symmetrical synovitis with pitting edema (RS3PE). All imAEs were treated with high-dose steroids. Symptoms improved to near complete resolution with high-dose steroids in the patient with optic neuritis and one patient with acute onset unilateral hearing loss, and to complete resolution in the patient with RS3PE. The second patient with acute onset unilateral hearing loss required use of a hearing aid. Durvalumab was discontinued in all patients who developed imAEs, but olaparib was continued. No patients were taken off-study due to toxicity. Patients received a median of 7 cycles of treatment (range: 2–17).(44)

4. BENEFIT/RISK AND ETHICAL ASSESSMENT

4.1 POTENTIAL BENEFITS

Durvalumab and Olaparib have been reported to have clinical activity in PCa patients with high neoantigen burden. Because durvalumab seems to be more effective in patients with high mutational burden, we expect that combining it with olaparib to activate immunogenic pathways (e.g. the STING pathway)(31–33) and

to impair DNA damage repair increasing mutational burden will potentiate the clinical effects of durvalumab — leading to durable PSA suppression. Potential benefit to participants could be postponing starting ADT and side effects associated with it. If effective, patients enrolled to this study would benefit by receiving an effective combination therapy that is otherwise unavailable. There may be no direct benefits to participants in this pilot study, however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe and effective intervention that prevents progression of metastasis in patients with biochemically recurrent prostate cancer and one of the genomic markers (lfCDK12, MMRd/MSI-high, HRD).

4.2 POTENTIAL RISKS

Potential risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies (hypo- and hyperthyroidism, type I diabetes mellitus (which may present as diabetic ketoacidosis), hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis), diabetes insipidus, noninfective encephalitis, pemphigoid, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, and infections/serious infections, and psoriasis.

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

Potential risks with olaparib include hematologic toxicities, infections associated with myelosuppression, gastrointestinal disorders. For information on all identified and potential risks with olaparib please refer to the current version of the olaparib IB. Please refer to Section 9, as well as olaparib and durvalumab IB for list of common toxicities. Additional important potential risks include infusion-related reactions, hypersensitivity, anaphylaxis or serious allergic reactions, serious infections, and immune complex disease. If the participant is sexually active and their female partner is of child-bearing potential, they must agree to use a medically acceptable form of birth control to reduce the potential for harm to an unborn child.

5. STUDY OBJECTIVES

As stated above, Durvalumab and Olaparib have been reported to have clinical activity in PCa patients with high neoantigen burden. Because durvalumab seems to be more effective in patients with high mutational burden, we expect that combining it with olaparib to impair DNA damage repair and increase mutational burden will potentiate the clinical effects of durvalumab — leading to durable PSA suppression. Potential benefit to participants could be postponing starting ADT and side effects associate with it. If effective, patients enrolled to this study would benefit by receiving an effective combination therapy that is otherwise unavailable.

5.1 PRIMARY OBJECTIVE(S)

- To assess clinical activity of durvalumab and olaparib in men with biochemically recurrent prostate cancer predicted to have a high neoantigen load

5.2 SECONDARY OBJECTIVE(S)

- Assess safety of durvalumab monotherapy
- Assess safety of durvalumab and olaparib combination therapy
- Assess PSA changes in relationship to intervention
- Assess quality of life changes

5.3 EXPLORATORY OBJECTIVE(S)

- Assess radiographic progression free survival (rPFS)
- Assess PSA progression free survival (PSA-PFS)
- Assess event free survival (EFS)
  Assess time to start of ADT

5.4 CORRELATIVE OBJECTIVE(S)

- identify favorable tumor microenvironment associated with response to durvalumab and olaparib
- identify genetic characteristics associated with response to durvalumab and olaparib
- to evaluate tumor clonal evolution
- evaluate systemic immune response at 3 and 6 months and at the time of progression

6. STUDY DESIGN

6.1 OVERVIEW OF STUDY DESIGN

This is a phase 2, open-label, single arm, three cohort, multicenter clinical trial. The trial will be conducted at two sites: 1) University of Washington Medical Center/Fred Hutchinson Cancer Center, and 2) Oregon Health and Sciences University (OHSU). This pilot clinical trial will test the clinical activity of durvalumab and olaparib in men with biochemically recurrent prostate cancer predicted to have a high neoantigen load inferred by the presence of either loss of function *CDK12* mutations (Cohort A) or MMRd/MSI-high (Cohort B) or HRD (Cohort C). Patients will be screened for these genomic markers as part of the trial and those identified will be enrolled in the respective cohort. We anticipate identifying the majority of the study cohort (~20) prior to screening; however, we are expecting to screen 50 patients without prior clinical sequencing to identify rest of the cohort (~10). Patients in cohort A and B will receive durvalumab monotherapy for 3 months followed by durvalumab plus olaparib for an additional 3 months. Patients in Cohort C will receive 6 months of durvalumab and olaparib combination therapy.

6.1.1 ENROLLMENT

This study will enroll men with biochemically recurrent prostate cancer who have received definitive local therapy (e.g. prostatectomy, radiation) and have a PSA doubling time ≤10 months, but no evidence of metastatic disease on conventional imaging (i.e. bone and CT scans). Note, patients with oligometastatic disease (i.e. ≤3 sites) detectable on advanced imaging only (e.g. PSMA or Fluciclovine PET) will still be eligible. If a study candidate did not have prior clinical grade NGS testing to assess for MMRd/MSI-high, lfCDK12 and HRD performed prior to screening for the study, archival tissue will be requested and sequenced using a clinical grade NGS assay and performed in a CLIA/CAP certified laboratory (e.g. FoundationOne, UW OncoPlex, etc.). If archival tissue is not available, cell-free circulating tumor DNA (ctDNA) may be used. Patients may be screened for neo-antigen burden after consent before meeting all other eligibility criteria.

6.1.2 TREATMENT

Following screening for eligibility and confirmation of genomic marker on screening, eligible patients will be assigned to the appropriate cohort (either A, B or C) and will receive durvalumab monotherapy for 3 months followed by combination of durvalumab and olaparib for 3 months Cohort A and B), or 6 months of combination therapy (Cohort C). Following the completion of the 6-month treatment period, patients will undergo monitoring for signs of PSA change, clinical and radiographic progression. Because observation is a reasonable option for prostate cancer patients with non-metastatic biochemical recurrence per NCCN guidelines, the study regimen will be given in the absence of androgen deprivation therapy.

6.1.3 MONITORING

Patients will be seen by research and oncology teams every 4 weeks while receiving durvalumab, and then every 3 months with PSA testing until completion of 24 months. Radiographic assessment (i.e., CT chest, abdomen and pelvis and bone scan) will be performed upon enrollment (within 6 weeks before study therapy start date) and then obtained as prompted by signs and symptoms of metastatic disease and/or at the time of PSA progression. Upon completion study visits (24 months from starting durvalumab) patients will continue to be followed as per standard of care. Clinical data after 24 months will be extracted from the clinical chart by the study team, as permitted by the patient. Patient will be followed passively through following clinical chart data up to 5 years total.

6.1.4 PROGRESSION

PSA progression will be defined as an increase in increase in PSA by 2 ng/ml and by 25% from baseline upon enrollment not earlier then 12 weeks after start of therapy, confirmed by repeat measurement at least 2 weeks later.

Radiographic metastatic progression will be defined per RECIST criteria and Prostate Cancer Working Group 3 (PCWG3) criteria, respectively(56,57). No confirmatory scan is required as enrolled patients had no previous metastatic disease.

Lymph Nodes

PCWG3 recommends that lymph nodes that were previously normal in size (< 1.0 cm) or pathologic in size must have grown by at least 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥ 1.5 cm in the short axis, it is pathologic and measurable. Nodes that have progressed to between 1.0 and less than 1.5 cm are pathologic subject to clinical discretion and are non-measurable.

Visceral
The date of first metastasis is the date on which an unequivocal visceral lesion by iRECIST is determined. Visceral disease should be reported as being with or without other patterns of spread (node, bone).

Bone
Documentation of radiographic evidence of metastatic disease should include the time of the unequivocal development of new sites on bone scintigraphy.

Use of Confirmatory Scans with Other Modalities
For patients who develop equivocal bone lesions while on study, PCWG3 discourages the use of other scanning modalities, including MRI, positron emission tomography, or other investigational scans that were not used to determine eligibility for the study. Supplemental scanning using imaging modalities with varied sensitivity that were selected by personal preference or regional practice may introduce bias.

6.1.5 ENDPOINTS

Cohorts A, B and C will be analyzed separately for all endpoints, except safety. Quality of life assessments for Cohort C will be analyzed separately, while quality of life data will be assessed separately and combined for Cohorts A and B.

Primary Endpoint(s):

- Undetectable PSA[1,2] (post-prostatectomy patients; including those that also received salvage radiation) or PSA <0.5 ng/ml[1] (post-radiation patients) at 12-month timepoint after initiation (cycle 1, day 1) of therapy.

Secondary Endpoint(s):

- Adverse events during durvalumab monotherapy per CTCAE v5.0 guidelines
- Adverse events during durvalumab and olaparib combination therapy per CTCAE v5.0 guidelines
- PSA50 response[1] (at least 50% decline in PSA from baseline at enrollment) at 3- and 6-month timepoints
- Quality of life changes using:
    a. RANDSF-36 two- step 8-scale score (see Appendix IV for algorithm) and
    b. IIEF surveys score in erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction (see Appendix VI for assessment details)

[1] confirmed by repeat measurement at least 2 weeks later
[2] Undetectable PSA defined as PSA <0.1 ng/ml

Exploratory Endpoint(s):

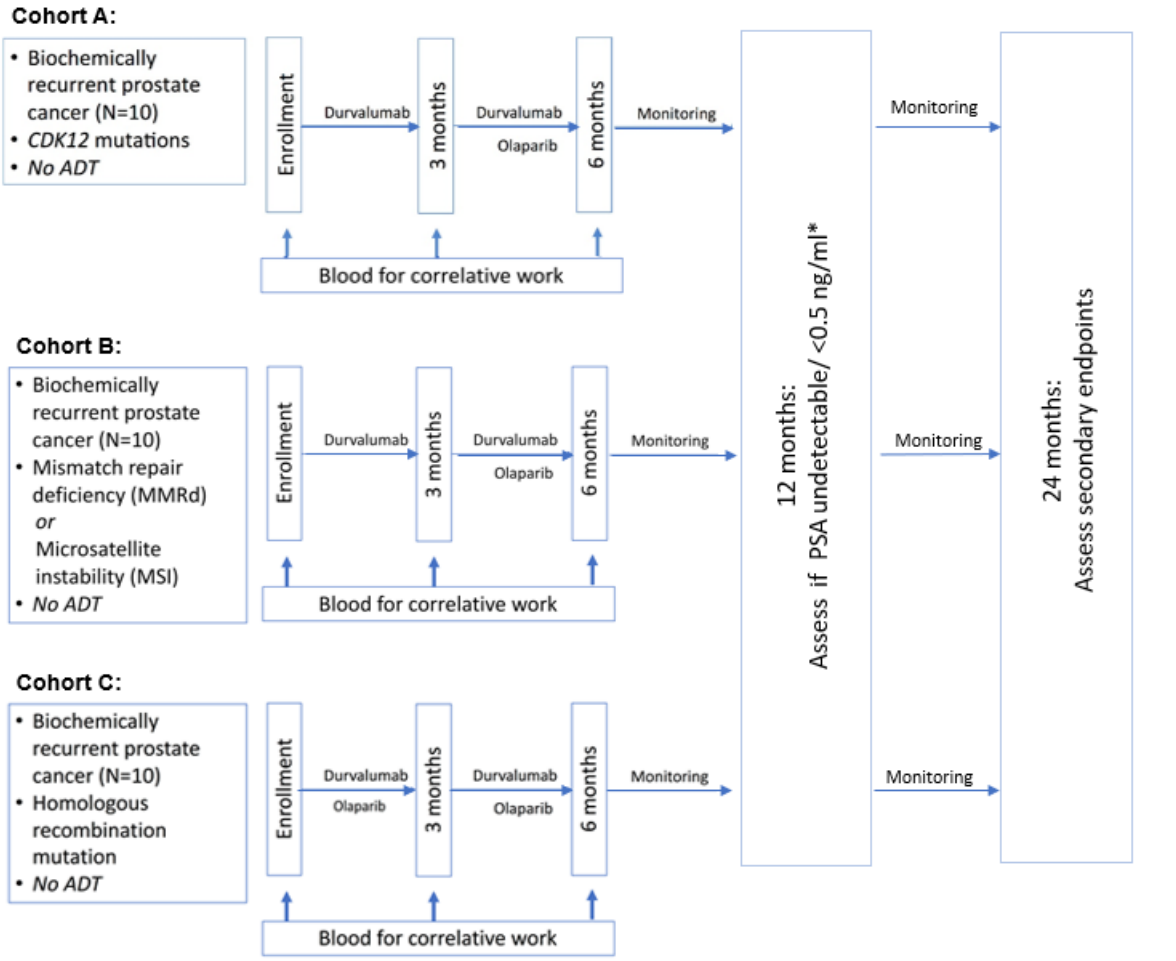
- rPFS, defined as time from enrollment to date of first objective radiographic evidence of metastatic disease (soft tissue or bone lesion) or death; in the absence of an event, PFS will be censored at date of last disease assessment
- PSA-PFS, defined as time from enrollment to PSA progression (increase in PSA by 2 ng/ml and by 25% from baseline/nadir), in the absence of an event, PSA-PFS will be censored at date of last disease assessment and/or visit documenting no next therapy.
- EFS; defined as time from enrollment to initiation of next line of therapy, development of metastatic disease or death; in the absence of an event, EFS is censored at date of last disease assessment and/or visit documenting no next therapy.
- Time to start of ADT; defined as time from enrollment to initiation of ADT; in the absence of an event, the endpoint is censored at date of last visit documenting no ADT initiation

Correlative Objectives and Endpoints:

1. **Objective**: identify favorable tumor microenvironment associated with response to durvalumab and olaparib
   Endpoint: CD8, CD4, FOXB3, PDL1 by IHC with quantitative output on archival prostate cancer tissue
2. **Objective**: identify genetic characteristics associated with response to durvalumab and olaparib
   Endpoint: number of somatic mutations, mutational signature, and DNA variants on whole exome or targeted gene sequencing of archival prostate cancer tissue
3. **Objective**: to evaluate tumor clonal evolution
   Endpoint: next generation sequencing of peripheral blood cell-free circulating tumor DNA (ctDNA) to evaluate mutational burden, and DNA variants in ctDNA at enrollment, at 6 months and at the time of progression
4. **Objective**: evaluate systemic immune response at 3 and 6 months and at the time of progression
   Endpoint: on peripheral blood measure cytokines using Cytokine Human Magnetic 35-Plex Panel for the Luminex™ platform; T-cells population using flow cytometry and T-cell receptor sequencing.

6.2 STUDY SCHEMA

Figure 1. ***Study Schema***



*Undetectable PSA for post-prostatectomy patients (including those that also received salvage radiation) or PSA <0.5 ng/ml for post-radiation patients

7. PATIENT SELECTION

7.1 INCLUSION CRITERIA

For inclusion in the study patients must fulfill all of the following criteria:

- Histologic confirmation of adenocarcinoma of the prostate
- The patient must have received definitive local therapy for prostate cancer, consisting of either radiation therapy and/or prostatectomy (salvage or adjuvant radiation post-prostatectomy is not exclusionary).

- PSA must be ≥2 ng/ml if received only prior definitive radiation (no PSA threshold required if prior prostatectomy was performed) with a PSA doubling time (PSADT) ≤10 months:
    - PSADT calculation must include all recorded PSA values >0.2 ng/ml over the past 6 months prior to randomization, with a minimum of 3 values spaced at least 2 weeks apart, with each included value preferably measured at the same laboratory. PSA values obtained prior to localized therapy will be excluded.
    - The calculation of PSADT is based on the natural log of PSA.
    - The actual calculation of the PSADT can be obtained from the following online calculator: http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx
- Prior salvage radiation or not a candidate for localized salvage radiation due to subject preference or clinical assessment based upon disease characteristics and/or subject co-morbidities
- Prior hormonal therapy (i.e., androgen deprivation therapy, oral AR-signaling inhibitors) is allowed, provided this was stopped ≥ 6 months prior to starting treatment per protocol, testosterone is ≥150 ng/dl and patient did not demonstrate evidence of castration-resistance while on hormonal therapy (i.e., PSA was not rising on treatment).
- No evidence of metastatic disease on imaging by whole body bone scan and CT or MRI of the chest/abdomen/pelvis within 6 weeks before study therapy start day. PSMA PET or Fluciclovine scan within 6 weeks of start day may substitute other imaging studies.
    - Patients with oligometastatic disease (i.e., ≤3 sites) detectable on advanced imaging only (e.g., PSMA or Fluciclovine PET) are eligible. Note: Prior site directed radiation is allowed; however, PSA must be rising following radiation as indicated above.
    - Abdominal or pelvic lymph nodes measuring ≤2 cm in short axis are allowed
- Biomarker positive:
    - Biallelic *CDK12* inactivating mutations as documented using a clinical grade sequencing assay performed in a CLIA/CAP certified laboratory

    or
    - MMRd/MSI-high as documented using a clinical grade assay performed in a CLIA/CAP certified laboratory

    or
    - Loss of function mutations in homologous recombination genes (i.e., homologous recombination deficiency; HRD) as documented using a clinical grade sequencing assay performed in a CLIA/CAP certified laboratory. Homologous recombination genes include, but not limited to *BRCA1, BRCA2, ATM, CHEK2, PALB2, RAD51D, NBN, GEN1, RAD51C, MRE11A, BRIP11A, FAM175A.*

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

- Age ≥ 18 years at time of study entry.

- Eastern Cooperative Oncology Group (ECOG) performance status of ≤1

- Adequate normal organ and marrow function as defined below measured within 28 days prior to administration of study treatment as defined below:

    - Hemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days

    - Absolute neutrophil count (ANC) be ≥1.5 x 10^9/L

    - Platelet count ≥100 x 10^9/L

    - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

    - AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN

    - Patient must have creatinine clearance (CL) ≥51 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

- Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

- Patients must have a life expectancy ≥ 16 weeks.

- Body weight >30 kg

- Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing

potential. Female partners of male patients should also use a highly effective form of contraception (Table10 for acceptable methods]) if they are of childbearing potential.

7.2 EXCLUSION CRITERIA

- Prior chemotherapy for prostate cancer, unless done in the neoadjuvant setting, and if the last dose was >6 months prior to enrolment
- Any prior treatment with a PD1 or PD-L1 inhibitor, including durvalumab
- Any prior treatment with a PARP inhibitor, including olaparib
- History of another primary malignancy except for
    - Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of durvalumab and of low potential risk for recurrence
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease
- History of leptomeningeal carcinomatosis
- Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the treating physician (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >470 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.
- Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or olaparib may be included only after consultation with the Study Physician.
- Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.
- Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not

limited to, extensive bilateral lung disease on High Resolution Computed Tomography (HRCT) scan, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea or any psychiatric disorder that prohibits obtaining informed consent.

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

- Immunocompromised patients, e.g., patients with uncontrolled human immunodeficiency virus (HIV). HIV+ patients will be allowed on the study if on HAART and disease is controlled: CD4≥350cell/mcl, undetectable viral load, and no PPX antibiotics.

  Note: HIV screening is not required to be eligible for this study.

- Active infection including **tuberculosis** (TB testing only performed if deemed necessary per standard clinical practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C.** Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

- 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:

  - Patients with vitiligo or alopecia

  - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

  - Any chronic skin condition that does not require systemic therapy

  - Patients without active disease in the last 5 years may be included but only after consultation with the Investigator

  - Patients with celiac disease controlled by diet alone

- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

  - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

  - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
  - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

- Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: Patients, if enrolled, should not receive live vaccine whilst receiving durvalumab and up to 30 days after the last dose of durvalumab.
- Patients receiving any chemotherapy, immunotherapy, biologic, radiotherapy or hormonal therapy for cancer treatment concurrently or within 3 weeks of study treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting *study treatment* is 2 weeks.
- Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil). The required washout period prior to starting *study treatment* is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
- Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
- Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
- Participation in another clinical study with an investigational product administered in the last 3 months
- Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) or supportive care, while on the clinical study or during the follow-up period of this interventional study
- Patients with a known hypersensitivity to olaparib or durvalumab or any of the excipients of the product.
- Involvement in the planning and/or conduct of the study

7.3 WITHDRAWAL OF PATIENTS FROM STUDY TREATMENT AND/OR STUDY

7.3.1 PERMANENT DISCONTINUATION OF STUDY TREATMENT

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event that, in the opinion of the Principal Investigator contraindicates further dosing
- Severe non-compliance with the study protocol that, in the opinion of the Principal Investigator or Sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits)
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Subject 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
- Initiation of alternative anticancer therapy including another investigational agent
- Study drug held for >4 weeks due to an AE

Patients who are permanently discontinued from further receipt of study treatment, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who have permanently discontinued treatment will enter follow-up (Section 10.1.3), including the collection of any protocol-specified blood specimens, unless consent is withdrawn, or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone as an alternative.

If a patient decides to voluntary discontinue durvalumab or olaparib, the reason(s) for discontinuation will be documented. Ideally, the patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who permanently discontinue the study treatment for reasons other than evidence of PSA progression or metastatic disease on conventional imaging should continue to have PSA monitoring q3 months for 24 months from the time of enrollment. iRECIST scans should be performed if increase in PSA by 2 ng/ml and by 25% from baseline upon enrollment.

If a patient is discontinued for iRECIST criteria, then the patient should have 1 additional follow-up scan performed preferably no less than 4 weeks after the prior assessment of disease.

Patients who decline to return to the site for evaluations should be contacted by telephone as an alternative.

7.3.2 LOST TO FOLLOW-UP

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Treating physician and Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

7.3.3 WITHDRAWAL OF CONSENT

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

Biospecimens obtained as part of trial participation will be retained.

7.4 ADDITIONAL PATIENT ENDROLLEMENT

To ensure that each cohort includes at least 10 patients that receive combination therapy, an additional patient will be accrued for every participant that drops out prior to receiving at least one cycle of combination therapy (i.e., one infusion of durvalumab and 28 days of olaparib). Patients that drop out will still be included in our assessment of the primary endpoint.

8. INVESTIGATIONAL PRODUCT(S)

Study drugs will be shipped from AstraZeneca to McKesson (Cary, NC), which will serve as central distributor to all study sites. The local investigational drug services (IDS) pharmacy will coordinate with the study investigator and/or research coordinator to order study drug shipments as needed. On treatment days, study drugs will be ordered per institutional SOPs and dispensed through IDS.

8.1 DURVALUMAB

8.1.1 DURVALUMAB FORMULATION/PACKAGING/STORAGE

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 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 and density of 1.054 g/mL. 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 original packaging until use to prevent prolonged light exposure.

8.1.2 DURVALUMAB DOSES AND TREATMENT REGIMENS

A durvalumab dose of 1500 mg (for patients >30 kg in weight) Q4W will be administered for total 6 cycles.

8.1.3 DURVALUMAB PREPARATION

Patients will receive 1500 mg durvalumab via IV infusion Q4W for 24 weeks (up to 6 doses/cycles) with the last administration on week 20, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If a patient's weight falls to 30 kg or below (≤30 kg) the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W.

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 to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL (i.e., 1500 mg) of durvalumab 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.

If weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Standard infusion time 1 hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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.

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

8.1.4 MONITORING OF DURVALUMAB DOSE ADMINISTRATION

Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

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 patients 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. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix VIII.

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 patients to an intensive care unit if necessary.

8.2 OLAPARIB

8.2.1 OLAPARIB FORMULATION/PACKAGING

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the investigator as round or oval green film coated tablet packed in high-density polyethylene (HDPE) bottles with child-resistant closures.

Investigational product	Dosage form and strength
Olaparib	*100 mg tablet*
Olaparib	*150 mg tablet*

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

8.2.2 OLAPARIB LABELLING

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language. Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrollment code (E-code) to be completed at the time of dispensing.

The label will include the following information:

- blank lines for quantity of tablets to be taken
- enrollment code (E-code)
- date of dispensing
- Instructions stating that the olaparib tablets should be taken at approximately the same time each morning and evening

8.2.3 OLAPARIB STORAGE

All study drugs should be kept in a secure place under appropriate storage conditions. For olaparib, the investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage.

8.2.4 OLAPARIB DOSES AND TREATMENT REGIMENS

An olaparib dose 300 mgs bid continually will be administered for three 28-day cycles (Cycle 4-6 in Cohort A and B; cycle 1-6 in Cohort C)

Each olaparib dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib will be dispensed to patients on Day 1 and every 28 days thereafter until the patient completes

the study, withdraws from the study or closure of the study. Study treatment is available as tablets containing 50mg of olaparib. Patients will be administered olaparib twice daily at 300 mgs bid continually. 300 mg olaparib should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food. 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 patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

8.2.5 OLAPARIB DOSE REDUCTION

In case a dose reduction is necessary (for reasons other than renal impairment or concomitant treatment with a moderate-strong CYP3A inhibitor), the Study treatment will be administered as follows:

Table 1 Dose reductions for olaparib to manage adverse events

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily (two x150 mg tablet twice daily)	250 mg twice daily (one 150 mg tablet and one 100 mg tablet twice daily)	200 mg twice daily (two x 100 mg tablet twice daily)

Table 2 Dose reduction for olaparib if patient develops moderate renal impairment

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

Table 3 Dose reductions for study treatment if patient has to start taking a strong or moderate CYP3A inhibitor

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

8.2.6 OLAPARIB COMPLIANCE

Patients will self-administer olaparib and record tablet administration in Pill Dairy (See Appendix VII). Study site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site.. All patients must return their bottle(s) of *olaparib* at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses.

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

The Investigational Product Storage Manager is responsible for managing the IMP from receipt by the study site until the destruction or return of all unused IMP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IMP.

9. TOXICITY MANAGEMENT GUIDELINES

9.1 DURVALUMAB TOXICITY GUIDELINES

AEs associated with durvalumab exposure may represent an immunologic etiology. These immune-related AEs (IMAEs) may occur shortly after the first dose or several months after the last dose of durvalumab treatment and may affect a single or multiple body systems simultaneously. Early recognition and management are critical to reduce complications. For suspected IMAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of IMAEs, withhold or permanently discontinue durvalumab and administer corticosteroids. Toxicity management guidelines, including when to withhold treatment are available from NCCN and ASCO and are recommended to be used to guide treatment decisions.(58,59) Specific trial guidelines are included in Appendix VII.

9.2 MANAGEMENT OF OLAPARIB TOXICITY

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Dose reduction below 200 mg twice daily will not be permitted. Once dose is reduced, escalation is not permitted.

9.2.1 Management of olaparib hematological toxicity

Management of anemia

Table 4 Management of anemia

Hemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Treating physician judgement to continue *olaparib* with supportive treatment (eg 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 Hb**< 10** *but* **≥ 9 g/dl** Treating physician judgement to continue *olaparib* with supportive treatment (e.g. transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If 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, management of anemia may require blood transfusions. For cases where patients 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.

Management of neutropenia, leukopenia, and thrombocytopenia

Table 5 Management of neutropenia, leukopenia, and thrombocytopenia

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

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the Treating physician with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

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

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

For cases where patients develop prolonged hematological toxicity (≥ 2-week interruption/delay in study treatment due to CTC grade 3 or worse), refer to guidance later in this section for the management of this.

Management of prolonged hematological toxicities while on olaparib treatment

If a patient develops prolonged hematological toxicity such as:

≥2 week interruption/delay in olaparib treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence

≥2 week interruption/delay in olaparib treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)

≥2 week interruption/delay in olaparib treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should

be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption.

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

9.2.2 Management of olaparib 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 study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Olaparib can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of study treatment.

9.2.3 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. From screening part onwards, should a patient develop nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs (see section 16.3) and appropriate treatment of the event given. 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 olaparib treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e., 2 pieces of toast or a couple of biscuits).

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

9.2.4 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with Investigator.

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

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

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

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

Table 6 Dose reductions for olaparib treatment

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

9.2.5 Management of renal impairment

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

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib 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 Treating physician should use his or her discretion in determining whether a dose change or discontinuation of olaparib is warranted.

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

9.3 COMBINATION TREATMENT REGIMEN WITH TOXICITY MANAGEMENT GUIDELINES

In addition to the individual toxicity management guidelines for durvalumab and olaparib described above, below outlined what actions are recommended for the management of any potential overlapping toxicities that may occur following treatment with this combination.

Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in both olaparib and durvalumab 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 durvalumab and olaparib study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified please follow durvalumab toxicity management protocol and continue holding both olaparib and durvalumab, discuss with the Investigator.

10. STUDY PROCEDURES

10.1 SCHEDULE OF STUDY PROCEDURES

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided in Appendix I.

10.1.1 SCREENING PHASE

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All patients must first read, understand, and sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window, except neo-antigen burden status (lfCDK12, MMRd/MSI-high, HRD) which can be determined at any point prior to enrolling on this trial, regardless of the date next-generation sequencing was performed or the date of tumor tissue acquisition used for this purpose. Patients may be screened for neo-antigen burden after consent before meeting all other eligibility criteria.

The following procedures will be performed during the Screening phase:

- Review of eligibility criteria
- Informed consent
- Medical history and demographics
- Full physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate if abnormal [2-5 minutes apart])
- Review of prior/concomitant medications

- RANDSF-36 QOL survey
- Calculate PSA doubling time
- IIEF QOL survey
- Review adverse events
- CT chest, abdomen, pelvis (completed within 6 weeks before C1D1 date)[1]

[1] Brain MRI will be performed only necessary if clinically indicated.

- Bone scan (completed within 6 weeks before C1D1 date)
- CDK12, MMRd/MSI-high, HRD screening (clinical grade sequencing assay of archival tissue or ctDNA performed in a CLIA/CAP certified laboratory)
- Clinical laboratory tests for:
  - Hematology (see Table 7)
  - Clinical chemistry (see Table 8)
  - TSH
  - Coagulation (PT, PTT, INR)
  - Creatinine Clearance
  - Hepatitis B and C serologies (HBsAg; anti–HCV antibody with reflexive an HCV RNA)
  - Testosterone
  - PSA
  - Urinalysis
  - Amylase
  - Lipase
  - Cortisol
  - Fasting lipid
  - Study correlates blood
    We will rely on past medical history and will not perform HIV screening for patients without known HIV infection.

Table 7. Hematology Laboratory Tests [a]

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 0), and as clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Each coagulation test result will be recorded in CRF.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Table 8. Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase [a]	Lactate dehydrogenase (LDH)
Alanine aminotransferase [a]	Lipase [b]
Amylase [b]	Magnesium (Mg) [c]
Aspartate aminotransferase [a]	Potassium
	Prostate specific antigen
Bicarbonate [c]	Sodium
Calcium	Testosterone (total and free)
Chloride [c]	Thyroid function test [e]
Creatinine [c d]	Total bilirubin[a]
Cortisol	Total protein
Fasting Lipids[f]	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyl transferase (GGT) [c]	Uric acid

[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. Hepatitis B and C serologies will be testing during screening phase.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyl transferase, and magnesium testing are to be performed at baseline, on Cycle 1 Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.

[d] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

[e] If TSH is measured within 14 days prior to Cycle 1 Day 1, it does not need to be repeated at Cycle 1 Day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

[f] Fasting lipids include Cholesterol (Total), Triglycerides, HDL, LDL, Non-HDL Cholesterol, Cholesterol/HDL Ratio

Table 9. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to Section 9 for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of study treatment.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 16.4.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study therapy must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

Subject Registration

Eligible patients will be entered on study centrally at the University of Washington by the Study Coordinator or Research Manager. To register a patient, the following documents should be completed and emailed to the Research Manager, Patrick Panlasigui at ppanlas2@seattlecca.org as well as the Study Coordinator Andrea Rivero at ariveroc@seattlecca.org at least 48 hours prior to any on study activities:

- Date of Birth
- Ethnicity and Race
- Copy of pathology report and other source documents verifying eligibility
- Signed participant consent form
- HIPAA authorization form (if separate from ICF)
- Completed eligibility checklist, signed by the local Investigator or Sub-Investigator

To complete the registration process, the Coordinating Site will:

- Review the registration packet and confirm eligibility
- Assign a participant screening/enrollment study number to all participants
- Send email confirmation regarding participant eligibility and registration status to the participating site

Signed ICFs must remain in each subject's chart and must be available for verification by monitors or regulatory agencies at any time.

NOTE: Confirmation of enrollment must be provided by the Coordinating Site before on-study activities may begin.

10.1.2 TREATMENT PHASE

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Appendix I). Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

Prior to each treatment cycle, enrolled eligible participants will undergo clinical assessment, medication review and toxicity screen with directed physical examination. Participants will also undergo laboratory assessment with CBC with differential, CMP, GGT, LDH, Mg and uric acid before each Day1 of each 4-week cycle treatment administration. Provided no dose limiting toxicity is identified, participants will proceed to receive study drug treatment as per administration instructions.

Prior to treatment cycle 4 and after cycle 6 (at 12 weeks and 24 weeks from C1D1, respectively), additional laboratory testing, including PSA, TSH, amylase, lipase and cortisol will be tested. An additional blood sample will also be collected for study correlates at baseline (i.e. within 72 hours before C1D1), 12 weeks and 24 weeks from C1D1. At these same visits, patients will also complete QOL assessment with RANDSF-36 and IIEF.

10.1.3 POST-TREATMENT FOLLOW-UP VISIT

Upon completion of treatment with the study drugs, enrolled participants will undergo follow-up every 12 weeks until 24 months from C1D1. Post-treatment visits will include clinical assessment, medication review, toxicity screen, directed physical examination, PSA testing and QOL assessment with RANDSF-36 and IIEF. At 12-month visit we will assess primary endpoint: undetectable PSA (post-prostatectomy patients; including those that also received salvage radiation) or PSA <0.5 ng/m (post-radiation patients).

10.1.4 24-MONTH END OF STUDY VISIT

An end of study visit will be undertaken at 24 months from C1D1. This visit will include clinical assessment, medication review, toxicity screen, as well as a directed physical examination, PSA testing and QOL assessment with RANDSF-36 and IIEF.

Follow-up after end of study visit at 24-months will be recommended to continue at every 12-week schedule (per Section 10.1.3) but will be deferred to patient and clinician discretion. If regular follow-up with study site will not continue, request will be made for patient to be followed passively by study coordinator and if approved by patient, patient contact and locator information should be collected. Passive follow-up will be planned to continue until disease progression or for 10 years from enrollment.

10.1.5 STUDY WITHDRAWAL VISIT

Patients withdrawing from the study prior to 24-months will undergo the procedures as follows depending on reason for withdrawal:

- If withdrawal is related to PSA progression, patients will undergo repeat imaging with CT chest, abdomen, pelvis and bone scan and study treatment will be discontinued. Decision to start ADT or alternate therapy will be deferred to patient and oncologist as is clinically appropriate. If no further therapy is initiated, patients will be followed per post-treatment follow-up schedule (Section 10.1.3). If ADT or alternate therapy is started, patient will be considered to not have achieved the primary endpoint at 12 months.
- If withdrawal is related to metastatic progression or ADT initiation, patients will be considered to not have achieved the primary endpoint at 12 months.
- If withdrawal is related to treatment toxicity, patients will be followed per post-treatment follow-up schedule (Section 10.1.3) until alternate therapy is initiated or until 24-month end of study visit. If patient develops metastatic disease or alternate therapy is initiated prior to 12-month visit, patients will be considered to not have achieved the primary endpoint at 12 months.

Participants who withdraw consent from the study prior to scheduled end date will be offered a study withdrawal visit. This visit will include a clinical assessment, medication review, toxicity screen, as well as a directed physical examination and PSA testing.

11. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

11.1 RESTRICTIONS DURING THE STUDY

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

- Grapefruit juice. It is prohibited to consume grapefruit juice while on olaparib therapy.
- Olaparib is regarded as a compound with medium/high fetal risk. Male patients with a female partner of childbearing potential
    - Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period and for 3 months following the last dose of olaparib or durvalumab.
    - Female partners (of childbearing potential) of male patients must use two highly effective methods of contraception in combination throughout this period and for 3 months following the last dose of olaparib or durvalumab (see table 10 below)

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Table 10. Highly Effective Methods of Contraception (<1% Failure Rate)

Non-hormonal Methods	Hormonal Methods
• 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 for 3 months after last dose. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception • Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia. • Tubal occlusion PLUS male condom IUD PLUS male condom. Provided coils are copper-banded	• Normal and low dose combined oral pills PLUS male condom • Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone-based pill. • Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom • Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom • Norelgestromin / EE transdermal system PLUS male condom • Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom Intravaginal device (e.g., EE and etonogestrel) PLUS male condom

Blood donation

Patients should not donate blood for at least 90 days following the last infusion of durvalumab or until after 4-5X the half-life of olaparib, whichever occurs longest.

11.2 CONCOMITANT TREATMENT(S)

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over the counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

Dosage information including dose and frequency

11.2.1 Permitted concomitant medications

Table 11. Supportive Medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Treating physician
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management (including palliative radiotherapy to non-target lesions, etc.)	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

11.2.2 Excluded concomitant medications

Table 12. Prohibited Concomitant Medications

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 patient 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 patient 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 patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable.

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 patients 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 patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).*
Live virus vaccines Live bacterial vaccines	Not permitted while the patient is receiving olaparib 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.
EGFR TKIs	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 sponsor

11.2.1 Restricted concomitant medications

Table 13 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir 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.
Strong inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with *olaparib.* If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy of *olaparib*

Table 13 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international 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.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 STATISTICAL CONSIDERATION

This is a multicenter pilot phase 2, prospective, single-arm, three cohort, open-label trial that will investigate the clinical activity of durvalumab and olaparib in men with BCR prostate cancer. Patients in Cohort A and B will receive durvalumab monotherapy for 3 months followed by durvalumab plus olaparib for an additional 3 months. Patients in Cohort C will receive 6 months of durvalumab and olaparib combination therapy.

To ensure that each cohort includes at least 10 patients that receive combination therapy, an additional patient will be accrued for every participant that drops out prior to receiving at least one cycle of combination therapy (i.e. one infusion of durvalumab and 28 days of olaparib). Patients that drop out will still be included in our assessment of the primary endpoint.

12.2 SAMPLE SIZE

Ten patients will be enrolled in each cohort (total 30). Within a given cohort, a response[1] rate of 30% or greater (response as defined in Section 6.1.5) would be a meaningful indicator of clinical activity and below 5% would be considered too low. The sample size was selected based on precision of a two-sided 90% confidence interval (CI) for the response rate; the exact binomial CIs for 0 to 5 responses among 10 patients are tabulated below. Observing 3 or more responses[1] among 10 patients would provide a two-sided 90% CI with lower confidence limit above 5%.

N. responses[1]	0	1	2	3	4	5
Response[1] rate	0%	10%	20%	30%	40%	50%
90% CI	0-25.9	0.5-39.4	3.7-50.7	8.7-60.7	15.0-69.7	22.2-77.8

[1]response as defined in Section 6.1.5

12.3 PRIMARY OBJECTIVES

The primary response endpoint is defined in Section 6.1.5. Separately by cohort, the response rate will be estimated as the number of patients who achieve response divided by the number of patients who initiate study therapy. If a patient starts new off study prostate cancer therapy before assessment of primary endpoint or withdraws consent or does not have adequate data to assess response, the patient will be included in the denominator and considered as not having response. The response rate will be reported with exact binomial two-sided 90% CI.

12.4 SECONDARY AND EXPLORATORY OBJECTIVES

Safety of durvalumab per CTCAE guidelines

Safety of durvalumab and olaparib combination per CTCAE guidelines

All patients who initiate study therapy will be evaluated for safety, combined across the three cohorts and separately for each cohort. Adverse events will be summarized as number (%) of patients by system organ class, CTCAE term and grade, where grade is the maximum across a patient's treatment period. The summaries will be separated for the cycles during which durvalumab monotherapy is administered and those during with the combination is administered. Only subjects who received at least one dose of durvalumab will be included in the safety analysis of durvalumab. Only subjects who received at least one dose of durvalumab and completed 2 weeks of olaparib will be included in the safety analysis of durvalumab and olaparib combination. The total sample size of 30 patients enrolled provides high probability of observing relatively rare AEs; there is 79% chance to observe at least one incidence of a specific AE if the true AE rate is 5%.

PSA50 Response

A descriptive summary (including the percentage and 90% CI) of PSA50 response rate (proportion of patients with a decline in PSA >50% from baseline) will be provided at 3- and 6-month timepoints. Subjects non-adherent to therapy will be followed to the end point at 3 and 6 - months per post treatment follow up. If a patient starts new off study prostate cancer therapy before assessment of endpoint or withdraws consent or does not have adequate data to assess response, the patient will be included in the denominator and considered as not having PSA50 response. The response rate will be reported with exact binomial two-sided 90% CI.

Quality of Life

Quality of life will be assessed at the time of enrollment and then every three months for 24 months. We will use the RANDSF-36 and International Index of Erectile Function (IIEF) score calculation (see appendix III-VI). Scores at different times will be compared for individual patients, and each patient will have his enrollment survey scores as the comparison. Overall change in study patients' QOL from time of enrollment to 6, 12, 18 and 24 months will be reported separately for Cohort C, while Cohorts A and B will report separately and combined. At the same time, for RANDSF-36, the mean, median, range and 95% CI of survey scores will be calculated every three months for enrolled patients. The trend of these means and 90% CI will be plotted by time.

For IIEF, a summary table for every three months including enrolled patients on trial be given as below

Function Domain	Max Score	Median Score	90% CI
A. Erectile Function (Q1,2,3,4,5,15)			
B. Orgasmic Function (Q9,10)			
C. Sexual Desire (Q11,12)			
D. Intercourse Satisfaction (Q6,7,8)			
E. Overall Satisfaction (Q13,14)			

rPFS, PSA-PFS, EFS and time to start of ADT

The endpoints are defined in Section 6.1.5. The distributions of each endpoint for each individual cohort will be estimated using Kaplan-Meier method. The 24-month and median times to event will be reported with 90% CI.

12.5 CORRELATIVE OBJECTIVES

Given our sample size no statistical test will be performed for correlative objectives. Association between tumor microenvironment (IHC score for CD8, CD4, FOXB3, PDL1) and primary endpoint will be described. We will also describe association between genetic characteristics (number of somatic mutations, mutational signature, and DNA variants) and primary endpoint will be described. We will describe immunologic response to treatments (level of cytokines in peripheral blood and % of T cell classes in peripheral blood and T-cell receptor sequencing) at baseline (i.e., within 72h of C1D1), 12 weeks and 24 weeks from C1D1. We will describe tumor clonal evaluation by comparing sequencing results on archival prostate cancer tissue or ctDNA at the time of enrollment to ctDNA at 6 months and at the time of progression.

12.6 STUDY ARM ASSIGNMENT

Upon confirmation of eligibility, patients will be stratified into three cohorts: CDK12 mutations in Cohort A, MMRd/MSI-high in Cohort B and HRD in Cohort C. There are three single arms without randomization. Patients in Cohort A and B will receive durvalumab monotherapy for 3 months followed by durvalumab plus olaparib for an additional 3 months. Patients in Cohort C will receive 6 months of durvalumab and olaparib combination therapy.

12.7 BLINDING

Since this is a three-cohort, single arm study, neither patients nor doctors will be blinded.

13. ASSESSMENT OF SAFETY

13.1 CLINICAL LABORATORY TESTS

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Treating physician and investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in Section 10.1.1, Table 7 (hematology), Table 8 (clinical chemistry), and Table 9 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies.

13.2 PHYSICAL EXAMINATIONS

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Focused physical examinations are to be utilized by the Treating physician on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 16.3.

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient 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 16.3.

At Screening, a single ECG will be obtained on which QTcF must be <470 ms.

13.3 VITAL SIGNS

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoAs. Body weight is also recorded at each visit along with vital signs.

First durvalumab infusion

On the first infusion day, patients will be monitored, and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients in the I-O arms before, during, and after each infusion at the following times (based on a 60-minute infusion):

Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])

Approximately 30 minutes during the infusion (**halfway** through infusion)

At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent durvalumab infusions

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated.

13.4 EARLY PATIENT REVIEW FOR SAFETY

It is recommended that patients are contacted 2 weeks after receiving every cycle of durvalumab (Cycle 1 Day 14, Cycle 2 Day 14, Cycle 3 Day 14, Cycle 4 Day 14, Cycle 5 Day 14, Cycle 6 Day 14) of study drug(s) to ensure early identification and management of toxicities.

13.5 ECOG PERFORMANCE STATUS

ECOG performance status will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (e.g., light housework or office work)

2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5. Dead

Any significant change from baseline or screening must be reported as an AE.

13.6 BONE MARROW OR BLOOD CYTOGENETIC ANALYSIS

Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for patients with prolonged hematological toxicities as defined in Section 9.2.1. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, olaparib should be discontinued and a full description of findings should be submitted with an SAE report by the Investigator to AstraZeneca Patient Safety for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.

13.7 OTHER SAFETY ASSESSMENTS

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 9.2) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [CT], blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

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

13.8 GENOMIC INSTABILITY STATUS

All patients will undergo targeted next-generation sequencing in order to evaluate for the presence of a CDK12 mutations, MMRd/MSI-high, HRD and other gene alterations at baseline. This will be accomplished using the UW OncoPlex platform, which has been validated for use with tumor tissue derived DNA and cell free tumor DNA (ctDNA)(60) or other certified next-generation sequencing (NGS) assay performed in a CLIA/CAP laboratory. Archival prostate cancer tissue will be requested for NGS. If archival tissue not available, or if a patient has a PSA >20 ng/mL, a plasma sample may be used for ctDNA sequencing.

Note: If prior to enrolling, a patient has already had their tumor sequenced using a next-generation sequencing assays performed in a CLIA/CAP certified laboratory (e.g., FoundationOne, Cans, etc.), these results may be used for determining of CDK12 mutations, MMRd/MSI-high, HRD mutational status.

13.9 EXPLORATORY BIOMARKERS

This study will incorporate a number of exploratory biomarkers. Given our rapidly evolving understanding of prostate cancer pathobiology and genetics, it is impossible to prospectively define all the relevant biomarkers for the patient population enrolled on this study. All samples will be collected at the timepoints indicated in Sections 10.1 of the protocol. Details regarding the collection, processing, shipping and storage of samples for exploratory research will be described in the Laboratory Manual. Examples of the studies to be conducted may include but will not be limited to those described below. Additional studies aimed at understanding response and resistance to the study drugs may be added as new information becomes available.

Protein expression studies

Protein expression studies will be conducted on circulating tumor cells (CTCs) and/or tumor tissue using immunofluorescence (IF) and immunohistochemistry (IHC), respectively. Expression of CD4, CD8, FOXb3 and PDL-1 as well as potentially other proteins will be assessed. IHC will be performed using commercially available antibodies and standard lab techniques. Cytokine Human Magnetic 35-Plex Panel for the Luminex™ platform will be used to measure cytokine levels in peripheral blood. CTCs for protein studies will be isolated using the RareCyte platform, which involves density-based enrichment followed IF staining and digital microscopy. (61)

Transcript profiling studies

Transcript profiling studies will be conducted on circulating tumor cells (CTCs) and/or tumor tissue. Transcript profiling on tumor tissue will be performed using RNA-seq, qRT-PCR or other gene expression profiling methods as appropriate (e.g., NanoString) and will follow standard lab techniques. AdnaTest will be used to isolate CTCs for transcript expression studies. AdnaTest isolates CTCs using antibody coated magnetic beads, which are designed to select populations of prostate cancer cells and is suitable for transcript profiling studies. Blood samples will be processed using AdnaTest and used for multiplexed qRT-PCR studies.

Next generation sequencing

NGS to identify CDK12, MMRd/MSI or HRD is required for eligibility (see Section 13.8). Additionally, number of somatic mutations, mutational signature, and DNA variants will be explored on whole exome sequencing of archival prostate cancer tissue or NGS panel of ctDNA. T-cell receptor sequencing might be performed as well. For schedule of ctDNA collection, please see Section 10.1

Flow cytometry
Flow cytometry or peripheral blood will be performed (schedule in Section 10.1) to evaluate T-cell populations.

13.10 PATIENT REPORTED OUTCOMES

The RANDSF-35 and IIEF quality of life questionnaires will be administered periodically throughout the duration of the study (Appendix III-VI). Patients will be provided with blank questionnaires and

encouraged to complete these at home prior to scheduled clinic visits as outlined in Sections 10.1. These may also be completed in the clinic if preferred by the patient. If completed at home, questionnaires must be completed within the time windows indicated in Sections 10.1.

14. BIOLOGICAL SAMPLING PROCEDURES

14.1 VOLUME OF BLOOD

Table 14 below provides an approximation of the amount of blood that will be drawn for the safety and biomarker assessments outlined in Sections 10.1. In general, these labs will not all be drawn at the same visit, and Table 14 provides an estimate for the upper limit of blood volume required from a patient at any given visit. The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on the study treatment becomes available. The total volume of blood that will be drawn from each subject in this study is as follows:

Table 14. Volume of Blood to be Drawn from Each Patients

Assessment		Sample volume (mL)	No of samples	Total volume (mL)
Safety[1]	Clinical chemistry	5	1	5
	Hematology	3	1	3
	Coagulation	3	1	3
	Hepatitis panel	5	1	5
Exploratory biomarker research	ctDNA studies	10	1	10
	Cytokines	5	1	5
	Flowcytometry	5	1	5
	Protein expression	5	1	5
Total		41	8	41

[1] The sample volumes for safety assessments are approximate volumes that are subject to change. Additional blood samples may be needed depending on the results of these studies and if patients require follow up testing or undergo additional procedures (e.g., fresh metastatic biopsy).

15. HANDLING, STORAGE AND DESTRUCTION OF BIOLOGICAL SAMPLES

Biospecimen samples will be stored for up to five years following the completion of this study. Samples will be stored at University of Washington and/or Fred Hutchinson Cancer Center (UW/FHCC). These samples may also be sent to our research partners participating in this study, including AstraZeneca. Specimens will not be used for reasons unrelated to this research study. All specimens will be kept in locked research laboratories at UW/FHCC. The use of these specimens will be supervised by the Investigator.

16. STUDY OVERSIGHT FOR SAFETY EVALUATION

16.1.1 DEFINITION OF ADVERSE EVENTS

The International Council 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 patient 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 patient's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the Treating physician, or a finding judged by the Treating physician 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 nontreatment emergent. A nontreatment-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 patient has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). 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.

16.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

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

- Results in death

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

> Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

Any new malignancy:

> Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
>
> The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

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

16.1.3 DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. AESI are defined as AEs that include, but are not limited to, events with a potential

inflammatory or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy.

If the Treating physician has any questions in regard to an event being an imAE, the Treating physician should promptly contact the Investigator.

AESIs observed with durvalumab include those listed below. Refer to the IB for complete details on the safety profile of durvalumab and incidence of observed AESI.

- Diarrhea / Colitis, intestinal perforation, enterocolitis, and proctitis
- 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
- Immune thrombocytopenia
- 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, vasculitis, non-infectious meningitis, non-infectious encephalitis, and psoriasis.

AESIs observed with durvalumab and olaparib combination include, but not limited to all of the above as well as:

- Anemia
- Leukopenia
- Lymphopenia
- Gastrointestinal disorders

- Infection

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 and olaparib Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (Section 9). These guidelines have been prepared by the AZ to assist the Treating physician and 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.

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (Section 9) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc.) will be captured eCRF.

It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

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

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan

(ii) Tumor markers: Particular tumor markers which are related to disease progression.

Additional Clinical chemistry: CRP, LDH

16.2 ASSESSMENT OF SAFETY PARAMETERS

16.2.1 ASSESSMENT OF SEVERITY

Assessment of severity is one of the responsibilities of the treating physician in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0.

The determination of severity for all other events not listed in the CTCAE should be made by the treating physician based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
Grade 4 (life-threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc.).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 16.4. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

16.3 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab or 30 days from last dose of olaparib, whatever comes later). If an event that starts post the defined safety, follow up period noted above is considered to be due to a late onset toxicity to study treatment then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the treating physician for as long as medically indicated, but without further recording in eCRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

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

- 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 (yes or no)
- 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 16.3.2.16.3.2
- Description of the SAE

The grading scales found in the NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

16.3.1 STUDY RECORDING PERIOD AND FOLLOW-UP FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure related SAEs must be captured until the patient is considered to have confirmed metastatic disease on conventional imaging and will have no further tumor assessments.

The treating physician is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

16.3.2 CAUSALITY COLLECTION

The treating physician will assess causal relationship between the IPs and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

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

A guide to the interpretation of the causality question is found in Section 9.

16.3.3 RELATIONSHIP TO PROTOCOL PROCEDURES

The treating physician is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of study treatment) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by treating physician s to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.

- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

16.3.4 ADVERSE EVENTS BASED ON SIGNS AND SYMPTOMS

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in eCRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

16.3.5 ADVERSE EVENTS BASED ON EXAMINATIONS AND TESTS

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IPs.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting treating physician should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

16.3.6 HY'S LAW

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as

SAEs. Please refer to Section 9 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

16.3.7 DISEASE PROGRESSION

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

16.3.8 NEW CANCERS

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

16.3.9 DEATHS

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in eCRF.

- The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in eCRF.

- A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the timeframes specified in Section 16.4

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

16.3.10 FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS

Any AEs that are unresolved at the patient's last visit in the study are followed up by the treating physician for as long as medically indicated, but without further recording in the eCRF.

After 90 days, only patients with ongoing investigational product related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

16.3.11 POST-STUDY EVENTS

After the patient has been permanently withdrawn from the study, there is no obligation for the treating physician to actively report information on new AE or SAEs occurring in former study patients after the 90-day since last durvalumab dose and 30-day since last olaparib dose. safety follow-up period. However, if a treating physician learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the treating physician should notify Investigator and AstraZeneca/MedImmune Patient Safety.

16.4 REPORTING OF SERIOUS ADVERSE EVENTS

All SAEs will be reported whether or not considered causally related to the investigational product, or to 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 durvalumab or 30 days after the last dose of olaparib or until the initiation of alternative anticancer therapy. The Investigator and/or treating physician 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 90 day follow up period should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

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

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

Otherwise, after study treatment completion (i.e., after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former

study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (90 days after the last dose of durvalumab or 30 days after the last dose of olaparib).

All serious, related and unexpected adverse events must be reported to AstraZeneca regardless of the country where the study is conducted.

For those events requiring expedited reporting to the regulatory authorities, the Investigator and/or treating physician must inform all applicable regulatory authorities (e.g., FDA), via a MedWatch/AdEERs or applicable required regulatory form (e.g., CIOMS), of any serious, related and unexpected adverse events in accordance with reporting obligations (e.g. FDA21 CFR 312.32) and will concurrently forward all such reports to AstraZeneca in English. A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca at the time the event is reported to the regulatory authorities (e.g., FDA). It is the responsibility of the Investigator to compile all necessary information and ensure that the regulatory authorities receive a report according with the applicable 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-19-14545**)

***** Investigator 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 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 regulatory authorities still needs to be reported to AstraZeneca 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.

Fred Hutch/UW is acting as the Coordinating Center for this multi-institutional study, therefore it is the responsibility of the Fred Hutch/UW Principal Investigator (or designee) to complete the Fred Hutch IRB Expedited Reporting Form for adverse events occurring at participating sites that meet the expedited reporting requirements. Expedited reporting includes all adverse events that are serious, related, and unexpected.

Any external sites that participate in the trial will obtain independent IRB approval and will be subject to the adverse event reporting policies of their independent institution and IRB. Participating institutions must report the AEs to the Coordinating Center following the Cancer Consortium IRB adverse event (AE) reporting guidelines. The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and will be responsible for communicating to all participating investigators, any observations reportable under the Cancer Consortium IRB Reporting Requirements. Participating Investigators will review any distributed AE reports, and will send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

16.4.1 REPORTING OF DEATHS TO ASTRAZENECA

All deaths must be recorded and reported as outlined in Section 16.4. In addition, all SAEs resulting in death or death of unknown cause must be reported to AstraZeneca via AEMailboxClinicalTrialTCS@astrazeneca.com within 7 calendar days of awareness or sooner when required (See Section 16.4).

Participating institutions must report the SAEs to both AstraZeneca and the Coordinating Center following the reporting guidelines above. The Coordinating Center will maintain documentation of all Participating Institution Serious Adverse Event reports and will be responsible for communicating to all participating investigators, any observations reportable under the Cancer Consortium IRB Reporting Requirements. Participating Investigators will review any distributed SAE reports, and will send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

16.4.2 OTHER EVENTS REQUIRING REPORTING

16.4.3 OVERDOSE

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

Any overdose of a study patient with durvalumab or olaparib, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the investigator. The investigator must report these to AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 16.4 for contact information) within 7 calendar days or sooner when required (see Section 16.4). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 16.4). 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 16.4). There is currently no specific treatment in the event of an overdose of durvalumab or olaparib. There is currently no specific treatment in the event of overdose with durvalumab or olaparib and possible symptoms of overdose are not established.

Olaparib and Durvalumab must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol

should be reported as an overdose. The Maximum Tolerated Dose is 300 mg twice daily for olaparib (tablet) and 20 mg/kg Q4W for durvalumab (IV).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately. The treating physician will use clinical judgment to treat any overdose.

16.4.4 HEPATIC FUNCTION ABNORMALITY

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the investigator. The Investigator must report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 16.4 for contact information) within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case are Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the treating physician.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the treating physician and evaluated by the investigator and AstraZeneca/MedImmune.

16.4.5 PATERNAL EXPOSURE

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab and at least for 90 days following the last dose of olaparib, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab and at least for 90 days following the last dose of olaparib, whichever is the longer time period should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the treating physician must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

16.4.6 MEDICATION ERROR

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those that lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the treating physician or other site personnel informs investigator within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The investigator works with the treating physician to ensure that all relevant information is completed within 1 or 5 calendar days. The investigator must report to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 16.4 for contact information) within 7 calendar days or sooner when required

(see Section 16.4) if there is an SAE associated with the medication error and within 30 days for all other medication errors.

16.5 SAFETY MONITORING

Sequential boundaries will be used to monitor rate of dose limiting toxicity (see definition Section 16.5.1) throughout the treatment period. The accrual will be paused if excessive numbers of dose limiting toxicity events is equal to or exceeds bn out of n patients with full follow-up (see Table 15). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 20% when the rate of dose limiting toxicity events is equal to the acceptable rate 30%. All patients that received at least one dose of durvalumab will be evaluated for safety using Pocock-type stopping boundary. Number of dose limiting toxicity incidents will be counted from start of monotherapy with durvalumab till completion of combination therapy with durvalumab and olaparib. Because enrollment is expected to proceed slowly, stopping boundaries will be assessed after each dose limiting toxicity event.

Table 15. Pocock-type stopping boundary for safety monitoring

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	4	5	5	6	6	6	7	7	8	8	8	9	9	10	10
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	10	11	11	11	12	12	12	13	13	14										

16.5.1 DOSE LIMITING TOXICITY DEFINITION

Dose limited toxicity defined as:
Hematologic toxicity:

- Grade ≥3 neutropenia complicated by fever >38.3°C
- Grade 4 neutropenia (lasting more than 7 days)
- Grade ≥3 thrombocytopenia with significant bleeding
- Grade 4 thrombocytopenia (regardless of duration)
- Grade 4 anemia (regardless of duration)
- Myelodysplastic syndrome
- Acute myeloid leukemia

Non-hematologic toxicity:

- Any Grade 4 non-immune-mediated AE
- Any Grade 4 immune-mediated AE, excluding endocrinopathies
- Any Grade 3 non-immune mediated AE that does not resolve to ≤Grade 1 or baseline within 30 days with optimal medical management
- Any Grade 3 immune-mediated AE – excluding diarrhea/colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/polymyositis, endocrinopathies and nephritis – that does not resolve to ≤Grade 1 or baseline within 30 days after onset of the event despite optimal medical management including systemic corticosteroids
- Grade 3 diarrhea or colitis that does not resolve to ≤Grade 1 within 14 days
  [*both* immune- *and* non-immune-mediated indicated here; the same is the case if not specified in remaining bullet points below]

- Grade 3 noninfectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
- **Aspartate** aminotransferase (AST) or **alanine** aminotransferase (ALT) ≥3×ULN with concurrent increase in total bilirubin (TBL) ≥2×ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver; i.e., "Hy's Law")
- ALT or AST >8×ULN or TBL>5×ULN
- Grade 3 immune-mediated rash that does not resolve to ≤Grade 1 or baseline within 30 days
- Grade 2 rash covering > 30% BSA that does not resolve to ≤Grade 1 or baseline within 30 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity (excluding Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome (such as Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within 3 days of initiating optimal medical management including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 30 days of initiating optimal medical management including systemic corticosteroids or that exhibits signs of respiratory insufficiency regardless of optimal medical management

Increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN

17. ETHICAL AND REGULATORY REQUIREMENTS

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Patient data protection.

This protocol and informed consent form(s) and any subsequent modifications — will be reviewed and approved by the Institutional Review Board Scientific Protocol Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/Ecs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/Ecs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

17.1 INFORMED CONSENT

Written informed consent will be obtained from each study participant (or the parents or legal guardians of participants who cannot consent for themselves). Each study site is responsible for developing a study informed consent form for local use, based on the coordinating center approved ICF and site local templates (if applicable), that describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their informed consent forms. Non-literate participants will be asked to document their informed consent by marking their informed consent forms (e.g., with an X, thumbprint, or other mark) in the presence of a literate third-party witness. Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants (or their parents or legal guardians) will be provided with a copy of their informed consent forms if they are willing to receive them.

17.2 INCENTIVES

Participants will not be compensated for trial participation. No travel reimbursement is provided.

17.3 CONFIDENTIALITY

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the investigators, AstraZeneca Pharmaceuticals and/or NIH.

17.4 CHANGES TO THE PROTOCOL AND INFORMED CONSENT FORM

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the Cancer Consortium IRB and Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

17.5 AUDITS AND INSPECTIONS

17.5.1 Documentation

Source documentation of clinical data will be stored at each participating site. The PI and study staff will maintain an electronic case report form (eCRF) database of all clinical data and additional study-related documentation will be maintained in a comprehensive and centralized filing system. Data entry into the eCRF will be performed at each participating site. These files will be suitable for inspection by AstraZeneca, the FDA, and/or other applicable regulatory agencies at any time. Documentation will consist of: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the FDA (as needed), IRB and sites; and drug accountability files, containing a complete account of the receipt and disposition of the study drug.

17.5.2 Access to Source Data

The PI will permit the Cancer Consortium representatives to monitor the study as frequently as deemed necessary to determine that protocol adherence and data recording are satisfactory. The eCRF and related source documents will be reviewed in detail at each site visit. Only original source documents are acceptable for review. Should the consortium or regulatory authorities select subjects at a participating site for review, said site will be required to provide electronic source documentation. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the eCRF, such as past history, secondary diagnoses, and concomitant medications. Other study records, such as correspondence with the IRB, and other committees, as well as screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of the FDA or other regulatory agencies.

18. STUDY MANAGEMENT

18.1 TRAINING OF STUDY SITE PERSONNEL

Prior to opening this study for accrual, each participating site will be required to have a Site Initiation Visit (SIV). The SIV will involve a presentation by the Investigator to review the protocol in detail. The SIV should be attended (in person or virtually) by the Investigator, study coordinator, investigational drug services representative and any other sub-investigators. If any of the aforementioned personnel are unable to attend the SIV, the participating site will be responsible for distributing the protocol and SIV presentation for review. Training should be documented on delegation logs at each participating site.

Before initiation of the study, the coordinating center will review and discuss the following items with the Investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, CRF/eCRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. Additional documents with instructions for study compliance and CRF/eCRF completion will be provided.

The following documentation required by the coordinating center must be received prior to initiation of the trial: curricula vitae of the PI and all Sub-Investigators; signed Protocol Agreement; copy of the correspondence from the IRB indicating approval of the protocol and Informed Consent Forms, signed by the IRB chairperson or designee; an IRB roster of the IRB members; copy of the Informed Consent Forms that were reviewed and approved by the IRB.

18.2 MONITORING OF THE STUDY

Trial monitoring will be in accordance with the Fred Hutchinson Cancer Center (FHCC)/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCC Scientific Review Committee (SRC) and the FHCC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Additionally, scheduled meetings will take place weekly and will include the Investigator (Michael Schweizer, MD), research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol. During these meetings the Sub-Investigators/ Investigator will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objective.

18.3 SOURCE DATA

Source data will be maintained in study binders or electronically in secure servers as appropriate. Servers will be maintained at FHCC/UWMC and any hard copies of source data will be kept in a locked office or locked filling cabinets.

18.4 STUDY TIMETABLE AND END OF STUDY

The end of the study is defined as the last visit of the last patient undergoing the study. The study also may be discontinued at any time by AstraZeneca Pharmaceuticals, the investigators, and/or the US Food and Drug Administration, and/or site IRBs/Ecs.

18.5 DATA MANAGEMENT

The Protocol Director, or her designees, will prepare and maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to analyze the study data. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

All data required by the trial will be entered onto paper and electronic case report forms. Any corrections to data required into the paper case report forms must be made in such a way that the original entry is not obscured. Only designated study staff will enter data for study participants after study visits. Case report forms will be checked against source document data by study staff.

Patient records will be kept in a secure location at the University of Washington accessible only to research authorized personnel. The patient identity will be kept as confidential as possible as required by law. Except as required by law, the patient will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Study subjects will be assigned an ID code. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, the patient identity will not be disclosed. The patient's personal data which may be included in the investigator's database shall be treated in compliance with all applicable laws and regulations.

Trial oversight will be carried out by the protocol director, Dr. Michael Schweizer, and his research staff. They will meet monthly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

19. STUDY GOVERNANCE AND OVERSIGHT

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

20. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

20.1 IDENTITY OF INVESTIGATIONAL PRODUCT(S)

Table 16. List of Investigational Products for This Study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	*50 mg/mL solution for infusion after dilution*	MedImmune/AstraZeneca
Olaparib	*100 mg tablet*	MedImmune/AstraZeneca
Olaparib	*150 mg tablet*	MedImmune/AstraZeneca

21. LIST OF REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.

2. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol. 2003 Feb;169(2):517–23.

3. Zietman AL, Chung CS, Coen JJ, Shipley WU. 10-year outcome for men with localized prostate cancer treated with external radiation therapy: results of a cohort study. J Urol. 2004 Jan;171(1):210–4.

4. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen M-H. Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J Urol. 2004 Nov;172(5 Pt 2):S42-46; discussion S46-47.

5. Prostate Cancer NCCN Guidlines Version 1.2019 03/06/2019.

6. Crook JM, O'Callaghan CJ, Duncan G, Dearnaley DP, Higano CS, Horwitz EM, et al. Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy. New England Journal of Medicine. 2012 Sep 6;367(10):895–903.

7. Downing A, Wright P, Hounsome L, Selby P, Wilding S, Watson E, et al. Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. Lancet Oncol. 2019 Mar;20(3):436–47.

8. Choi SM, Kam SC. Metabolic effects of androgen deprivation therapy. Korean J Urol. 2015 Jan;56(1):12–8.

9. Tae BS, Jeon BJ, Shin SH, Choi H, Bae JH, Park JY. Correlation of Androgen Deprivation Therapy with Cognitive Dysfunction in Patients with Prostate Cancer: A Nationwide Population-Based

Study Using the National Health Insurance Service Database. Cancer Res Treat. 2018 Jul 18;51(2):593–602.

10. Wallander M, Axelsson KF, Lundh D, Lorentzon M. Patients with prostate cancer and androgen deprivation therapy have increased risk of fractures—a study from the fractures and fall injuries in the elderly cohort (FRAILCO). Osteoporos Int. 2019 Jan 1;30(1):115–25.

11. Administration USFaD. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. In. 2017.

12. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017 28;357(6349):409–13.

13. Azad AA, Volik SV, Wyatt AW, Haegert A, Le Bihan S, Bell RH, et al. Androgen Receptor Gene Aberrations in Circulating Cell-Free DNA: Biomarkers of Therapeutic Resistance in Castration-Resistant Prostate Cancer. Clin Cancer Res. 2015 May 15;21(10):2315–24.

14. Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Vargas HA, et al. Analysis of the Prevalence of Microsatellite Instability in Prostate Cancer and Response to Immune Checkpoint Blockade. JAMA Oncol. 2018 Dec 27;

15. Schweizer MT, Drake CG. Immunotherapy for prostate cancer: recent developments and future challenges. Cancer Metastasis Rev. 2014 Sep;33(2–3):641–55.

16. PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma | NEJM [Internet]. [cited 2019 May 26]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1411087

17. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123–35.

18. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015 May 21;372(21):2018–28.

19. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Jul 2;373(1):23–34.

20. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015 Jun 25;372(26):2509–20.

21. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372(26):2521–32.

22. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma. New England Journal of Medicine. 2014 Dec 4;371(23):2189–99.

23. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer genome landscapes. Science. 2013 Mar 29;339(6127):1546–58.

24. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017 07;389(10064):67–76.

25. Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody. Cancer Immunol Res. 2015 Sep;3(9):1052–62.

26. Graff JN, Alumkal JJ, Drake CG, Thomas GV, Redmond WL, Farhad M, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget. 2016 Jul 12;7(33):52810–7.

27. Mateo J, Carreira S, Seed G, Chandler R, Dolling D, Figueiredo I, et al. Genomic profiling of primary prostate tumors from patients who develop metastatic castration-resistant prostate cancer (mCRPC). JCO. 2018 May 20;36(15_suppl):5013–5013.

28. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035):913–7.

29. Lomonosov M, Anand S, Sangrithi M, Davies R, Venkitaraman AR. Stabilization of stalled DNA replication forks by the BRCA2 breast cancer susceptibility protein. Genes Dev. 2003 Dec 15;17(24):3017–22.

30. Arnaudeau C, Lundin C, Helleday T. DNA double-strand breaks associated with replication forks are predominantly repaired by homologous recombination involving an exchange mechanism in mammalian cells. J Mol Biol. 2001 Apr 13;307(5):1235–45.

31. Barber GN. STING: infection, inflammation and cancer. Nat Rev Immunol. 2015 Dec;15(12):760–70.

32. Woo S-R, Fuertes MB, Corrales L, Spranger S, Furdyna MJ, Leung MYK, et al. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. Immunity. 2014 Nov 20;41(5):830–42.

33. Klarquist J, Hennies CM, Lehn MA, Reboulet RA, Feau S, Janssen EM. STING-mediated DNA sensing promotes antitumor and autoimmune responses to dying cells. J Immunol. 2014 Dec 15;193(12):6124–34.

34. Juan H-C, Lin Y, Chen H-R, Fann M-J. Cdk12 is essential for embryonic development and the maintenance of genomic stability. Cell Death Differ. 2016;23(6):1038–48.

35. Blazek D, Kohoutek J, Bartholomeeusen K, Johansen E, Hulinkova P, Luo Z, et al. The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. Genes Dev. 2011 Oct 15;25(20):2158–72.

36. Joshi PM, Sutor SL, Huntoon CJ, Karnitz LM. Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. J Biol Chem. 2014 Mar 28;289(13):9247–53.

37. Ekumi KM, Paculova H, Lenasi T, Pospichalova V, Bösken CA, Rybarikova J, et al. Ovarian carcinoma CDK12 mutations misregulate expression of DNA repair genes via deficient formation and function of the Cdk12/CycK complex. Nucleic Acids Res. 2015 Mar 11;43(5):2575–89.

38. Bajrami I, Frankum JR, Konde A, Miller RE, Rehman FL, Brough R, et al. Genome-wide profiling of genetic synthetic lethality identifies CDK12 as a novel determinant of PARP1/2 inhibitor sensitivity. Cancer Res. 2014 Jan 1;74(1):287–97.

39. De Bono JS, Goh JC, Ojamaa K, Piulats Rodriguez JM, Drake CG, Hoimes CJ, et al. KEYNOTE-199: Pembrolizumab (pembro) for docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). JCO. 2018 May 20;36(15_suppl):5007–5007.

40. Meeting Library | Initial results from a phase II study of nivolumab (NIVO) plus ipilimumab (IPI) for the treatment of metastatic castration-resistant prostate cancer (mCRPC; CheckMate 650). [Internet]. [cited 2019 May 18]. Available from: https://meetinglibrary.asco.org/record/169424/abstract

41. Robinson D, Van Allen EM, Wu Y-M, Schultz N, Lonigro RJ, Mosquera J-M, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015 May 21;161(5):1215–28.

42. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. New England Journal of Medicine. 2016 Aug 4;375(5):443–53.

43. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. New England Journal of Medicine. 2015 Oct 29;373(18):1697–708.

44. Karzai F, VanderWeele D, Madan RA, Owens H, Cordes LM, Hankin A, et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. J Immunother Cancer [Internet]. 2018 Dec 4 [cited 2019 May 2];6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6280368/

45. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer | NEJM [Internet]. [cited 2019 May 18]. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1200690

46. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee J-L, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 16;376(11):1015–26.

47. Lipson EJ, Forde PM, Hammers H-J, Emens LA, Taube JM, Topalian SL. Antagonists of PD-1 and PD-L1 in Cancer Treatment. Semin Oncol. 2015 Aug;42(4):587–600.

48. Lim DM, Gulati R, Aleshin-Guendel S, Gawne A, Wingate JT, Cheng HH, et al. Undetectable prostate-specific antigen after short-course androgen deprivation therapy for biochemically

recurrent patients correlates with metastasis-free survival and prostate cancer-specific survival. The Prostate. 2018;78(14):1077–83.

49. Critz FA, Levinson AK, Williams WH, Holladay DA, Holladay CT. The PSA nadir that indicates potential cure after radiotherapy for prostate cancer. Urology. 1997 Mar;49(3):322–6.

50. Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012 Jan;52(1):18–28.

51. Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-α monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet. 2013 Nov;52(11):1017–27.

52. Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009 Sep;49(9):1012–24.

53. Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006 Jun;23(6):1275–84.

54. Joaquin Mateo. TOPARP-B: A phase II randomized trial of the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration resistant prostate cancers (mCRPC) with DNA damage repair (DDR) alterations. J Clin Oncol 37, 2019 (suppl; abstr 5005).

55. Abida W., et al. Preliminary Results from TRITON2: A Phase 2 Study of Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Repair (HRR) Gene Alterations" (abstract 793PD), ESMO 2018.

56. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143–52.

57. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Grou... - PubMed - NCBI [Internet]. [cited 2019 May 18]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26903579

58. National Comprehensive Cancer Network. NCCN IRAE guidelines [Internet]. Management of Immunotherapy-related toxicities. [cited 2019 May 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

59. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. JCO. 2018 Feb 14;36(17):1714–68.

60. Validation and implementation of targeted capture and sequencing for the detection of actionable mutation, copy number variation, and gene rearrang... - PubMed - NCBI [Internet]. [cited 2019 Aug 1]. Available from: https://www-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/pubmed/24189654

61. High-recovery visual identification and single-cell retrieval of circulating tumor cells for genomic analysis using a dual-technology platform inte... - PubMed - NCBI [Internet]. [cited 2019 Aug 1]. Available from: https://www-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/pubmed/25944336

62. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997 Jun;49(6):822–30.

22. APPENDICES

I. SCHEDULE OF STUDY VISITS AND PROCEDURES

I. SCHEDULE OF STUDY VISITS AND PROCEDURES

Trial Period:	**Screening**	**Treatment**						**Post-Treatment**			
Trial Phase/Cycle:	Pre-treatment	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	Follow-up visits[7]	12-month follow-up	Post 12-month Follow-up visits[7]	24-month follow-up[12]
Scheduling Window:	-28 to -1	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	Every 12 weeks	(12 months from C1D1 ± 3 days)	Every 12 weeks	(24 months from C1D1 ± 3 days)
Study informed consent[0]	X										
Inclusion/Exclusion criteria	X										
Demographics and medical history	X[2]										
Calculate PSA doubling time	X[3]										
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Review adverse events	X	X	X	X	X	X	X	X	X	X	X
RANDSF-36 QOL survey	X				X			X	X	X	X
IIEF QOL survey	X				X			X	X	X	X
Full physical examination	X										
Targeted physical examination		X	X	X	X	X	X	X	X	X	X
Vital signs and weight	X	X	X	X	X	X	X	X	X		X
ECG[8]	X	As clinically indicated									
ECOG performance status	X	X	X	X	X	X	X	X	X		X
CT chest, abdomen, pelvis	X[4]	Repeat if increase in PSA by 2 ng/ml and by 25% from baseline not earlier then 12 weeks after start of therapy, confirmed by repeat measurement at least 2 weeks later									
Bone scan	X[4]										
CDK12, MMRd/MSI-high, HRD screening[1]	X										

I. SCHEDULE OF STUDY VISITS AND PROCEDURES

Trial Period:		**Screening**	**Treatment**						**Post-Treatment**			
Trial Phase/Cycle:		Pre-treatment	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	Follow-up visits[7]	12-month follow-up	Post 12-month Follow-up visits[7]	24-month follow-up[12]
PSA[5]		X[5]				X			X	X	X	X
Testosterone (total and free)		X										
PT/INR and aPTT[10]		X										
CBC with differential		X	X	X	X	X	X	X		X		
Comprehensive serum chemistry panel[11]		X	X	X	X	X	X	X	X	X		
Lactate dehydrogenase		X	X	X	X	X	X	X		X		
Uric Acid		X	X	X	X	X	X	X		X		
Magnesium		X	X	X	X	X	X	X		X		
GGT		X	X	X	X	X	X	X		X		
Urinalysis		X										
TSH[6]		X				X			X[6]	X		
Amylase and Lipase[6]		X				X			X[6]	X		
Cortisol[6]		X				X			X[6]	X		
Fasting lipid panel		X										
Hepatitis B and C[9]		X										
Study correlates blood		X				X			X			
Archival tumor IHC for study correlates		X										
Patient follow-up contact / Patient review for safety			Day 14 (+/- 3 days) of Cycles 1, 2, 3, 4, 5, 6									
Durvalumab administration			X	X	X	X	X	X				
Olaparib dispensation	Cohort A & B					X	X	X				
	Cohort C		X	X	X	X	X	X				

C-cycle
0 If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.

1Screening specifications per Section 10.1.1
2 Record date of diagnosis, stage and primary treatment history
3 Can be obtained from following online calculator: http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx
4 Within 6 weeks before study therapy start day. For patients that don't have imaging done before consent, it will be done on the study after confirmation of lfCDK12 or MMRd/MSI-high or HRD eligibility
5 Repeat PSA only if >28 days from screening PSA/most recent PSA.
6 TSH, amylase, lipase and cortisol need only be checked at pre-treatment, 3, 6, 9 and 12 months (not necessary for every 12 weeks after 12 months)
7 First follow-up visit will be 2 weeks after last treatment dose for 24-week PSA and QOL survey
8 Any clinically significant abnormalities detected require triplicate ECG (electrocardiogram) results
9 HBsAg; anti–HCV antibody with reflexive an HCV RNA
10 For patients on warfarin INR be monitored at least once per week for the first month, then monthly if the INR is stable
11 Creatinine clearance will be measured by Cockcroft-Gault equation or based on a 24-hour urine test. 24 urine test could be added at any point CMP is performed at the discretion on Study Physician.
12 Participants who withdraw consent from the study prior to scheduled end date will be offered a study withdrawal visit and will have all evaluations planned to be performed at 24-month follow up visit and also have CMP at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of study treatment.

II. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

III. RANDSF-36 SURVEY

SF-36 Survey

Date: / / Patient's Name

Visit: □ baseline ☐ 3 month □ 6 month □ 9 month □ 12 month

INSTRUCTIONS: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by circling the number that best represents your response.

1. In general, would you say your health is?

Excellent (1)	Very Good (2)	Good (3)	Fair (4)	Poor (5)

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago

(1)	(2)	(3)	(4)	(5)

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much: (circle one number on each line)

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
A. **Vigorous activities**, such as running, lifting heavy objects participating in strenuous sports	1	2	3
B. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
C. Lifting or carrying groceries	1	2	3
D. Climbing **several** flights of stairs	1	2	3
E. Climbing **one** flight of stairs	1	2	3
F. Bending, kneeling, or stooping	1	2	3
G. Walking **more than a mile**	1	2	3
H. Walking **several hundred yards**	1	2	3
I. Walking **one hundred yards**	1	2	3
J. Bathing or dressing yourself	1	2	3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health?</u> (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	A **little** of the time	**None** of the time
A. Cut down on the **amount of time** you spend on work or other activities	1	2	3	4	5
B. **Accomplished less** than you would like	1	2	3	4	5
C. Were limited in the **kind** of work or other activities	1	2	3	4	5
D. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)? (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	**A little** of the time	**None** of the time

A. Cut down on the **amount of time** you spend on work or other activities	1	2	3	4	5
B. **Accomplished less** than you would like	1	2	3	4	5
C. Did work or activities **less carefully than usual**	1	2	3	4	5

6. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your social activities with family, friends, neighbors, or groups? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>? (Circle one)

None (1)	Very Mild (2)	Mild (3)	Moderate (4)	Severe (5)	Very Severe (6)

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	**A little** of the time	**None** of the time
A. did you feel full of life?	1	2	3	4	5
B. have you been very nervous?	1	2	3	4	5
C. have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5
D. have you felt calm and peaceful?	1	2	3	4	5
E. did you have a lot of energy?	1	2	3	4	5
F. have you felt downhearted and depressed?	1	2	3	4	5
G. did you feel worn out?	1	2	3	4	5
H. have you been happy?	1	2	3	4	5
I. did you feel tired?	1	2	3	4	5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the Time (1)	Most of the Time (2)	Some of the Time (3)	A Little of the Time (4)	None of the Time (5)

11. How TRUE or FALSE is each of the following statements for you? (Circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
A. I seem to get sick a little easier than other people	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

IV. RANDSF-36 SURVEY SCORING

Scoring the RAND 36-Item Health Survey is a two-step process. First, precoded numeric values are recoded per the scoring key given in Table 17. Note that all items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved. In step 2, items in the same scale are averaged together to create the 8 scale scores. Table3 lists the items averaged together to create each scale. Items that are left blank

(missing data) are not taken into account when calculating the scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered.

Example: Items 20 and 32 are used to score the measure of social functioning. Each of the two items has 5 response choices. However, a high score (response choice 5) on item 20 indicates the presence of limitations in social functioning, while a high score (response choice 5) on item 32 indicates the absence of limitations in social functioning. To score both items in the same direction, Table 17 shows that responses 1 through 5 for item 20 should be recoded to values of 100, 75, 50, 25, and 0, respectively. Responses 1 through 5 for item 32 should be recoded to values of 0, 25, 50, 75, and 100, respectively. Table 18 shows that these two recoded items should be averaged together to form the social functioning scale. If the respondent is missing one of the two items, the person's score will be equal to that of the non-missing item.

Table 19 presents information on the reliability, central tendency, and variability of the scales scored using this method.

Table 17. Step 1: Recoding Items

Item numbers	Change original response category *	To recoded value of:
1, 2, 20, 22, 34, 36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 →	0
	2 →	50
	3 →	100

13, 14, 15, 16, 17, 18, 19	1 →	0
	2 →	100
21, 23, 26, 27, 30	1 →	100
	2 →	80
	3 →	60
	4 →	40
	5 →	20
	6 →	0
24, 25, 28, 29, 31	1 →	0
	2 →	20
	3 →	40
	4 →	60
	5 →	80
	6 →	100
32, 33, 35	1 →	0
	2 →	25

	3 →	50
	4 →	75
	5 →	100

* Precoded response choices as printed in the questionnaire.

Table 18

Step 2: Averaging Items to Form Scales

Scale	Number of items	After recoding per Table 1, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	4	13 14 15 16
Role limitations due to emotional problems	3	17 18 19
Energy/fatigue	4	23 27 29 31
Emotional well-being	5	24 25 26 28 30
Social functioning	2	20 32
Pain	2	21 22

General health	5	1 33 34 35 36

Table 19

Reliability, Central Tendency, and Variability of Scales in the Medical Outcomes Study

Scale	Items	Alpha	Mean	SD
Physical functioning	10	0.93	70.61	27.42
Role functioning/physical	4	0.84	52.97	40.78
Role functioning/emotional	3	0.83	65.78	40.71
Energy/fatigue	4	0.86	52.15	22.39
Emotional well-being	5	0.90	70.38	21.97
Social functioning	2	0.85	78.77	25.43
Pain	2	0.78	70.77	25.46
General health	5	0.78	56.99	21.11
Health change	1	—	59.14	23.12

V. INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

These questions ask about the effects that your erection problems have had on your sex life over the last four weeks. Please try to answer the questions as honestly and as clearly as you are able. Your answers will help your doctor to choose the most effective treatment suited to your condition. In answering the questions, the following definitions apply: - sexual activity includes intercourse, caressing, foreplay & masturbation - sexual intercourse is defined as sexual penetration of your partner - sexual stimulation includes situation such as foreplay, erotic pictures etc. - ejaculation is the ejection of semen from the penis (or the feeling of this) - orgasm is the fulfilment or climax following sexual stimulation or intercourse

OVER THE PAST 4 WEEKS CHECK ONE BOX ONLY		
□ Q1	How often were you able to get an erection during sexual activity?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
□ Q2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always

□ Q3	When you attempted intercourse, how often were you able to penetrate (enter) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
□ Q4	During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
□ Q5	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time)

		5 Almost always or always
□ Q6	How many times have you attempted sexual intercourse?	0 No attempts 1 One to two attempts 2 Three to four attempts 3 Five to six attempts 4 Seven to ten attempts 5 Eleven or more attempts
□ Q7	When you attempted sexual intercourse, how often was it satisfactory for you?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
□ Q8	How much have you enjoyed sexual intercourse?	0 No intercourse 1 No enjoyment at all 2 Not very enjoyable 3 Fairly enjoyable

		4 Highly enjoyable 5 Very highly enjoyable
□ Q9	When you had sexual stimulation or intercourse, how often did you ejaculate?	0 No sexual stimulation or intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
□ Q10	When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
□ Q11	How often have you felt sexual desire?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time)

		5 Almost always or always
□ Q12	How would you rate your level of sexual desire?	1 Very low or none at all 2 Low 3 Moderate 4 High 5 Very high
□ Q13	How satisfied have you been with your overall sex life?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
□ Q14	How satisfied have you been with your sexual relationship with your partner?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied

□ Q15	How do you rate your confidence that you could get and keep an erection?	1 Very low 2 Low 3 Moderate 4 High 5 Very high

VI. ASSESMENT OF INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

The 15-question International Index of Erectile Function (IIEF) Questionnaire is a validated, multidimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials. A score of 0-5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction. Scores are awarded according to the number 0-5 next to the answer, the higher the score the more distress patient is experiencing.

In a study,(62) the IIEF Questionnaire was tested in a series of 111 men with sexual dysfunction and 109 age-matched, normal volunteers. The following mean scores were recorded:

FUNCTION DOMAIN	MAX SCORE	CONTROLS	PATIENTS
A. Erectile Function (Q1,2,3,4,5,15)	30	25.8	10.7
B. Orgasmic Function (Q9,10)	10	9.8	5.3
C. Sexual Desire (Q11,12)	10	7.0	6.3
D. Intercourse Satisfaction (Q6,7,8)	15	10.6	5.5
E. Overall Satisfaction (Q13,14)	10	8.6	4.4

VII. PILL DIARY

Durvalumab and Olaparib for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a multicenter pilot phase 2 study

Dates _____/_____/_____ to _____/_____/_____ Cycle #: _____

Subject ID: _____ Patient Initials: _____

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT

Instructions for olaparib tablets:

- should be taken at the dose of _____ twice a day orally
- should be taken at the same time each day, approximately 12 hours apart with one glass of water
- should be swallowed whole and not chewed, crushed, dissolved or divided
- can be taken with or without food
- if vomiting occurs shortly after the olaparib tablets are swallowed, and all intact tablets can be seen and counted in the vomit, take the dose again
- if you miss a scheduled dose, you may take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take usual dose at the next scheduled time.

Please return all unused study medication to your research nurse.

Please complete this section for your current cycle.

Day	Date	Did you take your AM dose of agent (circle YES or NO)	Did you take your PM dose of agent (circle YES or NO)
Example	**1/1/2016**	**YES / NO**	**YES / NO**
1		**YES / NO**	**YES / NO**
2		**YES / NO**	**YES / NO**
3		**YES / NO**	**YES / NO**
4		**YES / NO**	**YES / NO**

5		**YES / NO**	**YES / NO**
6		**YES / NO**	**YES / NO**
7		**YES / NO**	**YES / NO**
8		**YES / NO**	**YES / NO**
9		**YES / NO**	**YES / NO**
10		**YES / NO**	**YES / NO**
11		**YES / NO**	**YES / NO**
12		**YES / NO**	**YES / NO**
13		**YES / NO**	**YES / NO**
14		**YES / NO**	**YES / NO**
15		**YES / NO**	**YES / NO**
16		**YES / NO**	**YES / NO**
17		**YES / NO**	**YES / NO**
18		**YES / NO**	**YES / NO**
19		**YES / NO**	**YES / NO**
20		**YES / NO**	**YES / NO**
21		**YES / NO**	**YES / NO**

22		**YES / NO**	**YES / NO**
23		**YES / NO**	**YES / NO**
24		**YES / NO**	**YES / NO**
25		**YES / NO**	**YES / NO**
26		**YES / NO**	**YES / NO**
27		**YES / NO**	**YES / NO**
28		**YES / NO**	**YES / NO**

Patient Signature: _____

Date: _____

MD/RN Signature: _____

Date: _____

Comments:_____
_____
_____

VIII. DURVALUMAB TOXICITY MANAGEMENT GUIDELINE TABLES

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 28 October 2022

General Considerations regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.
Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long- term steroid and other immunosuppressive use, consider the need for glucose monitoring. Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation
- Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy
- Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines**.**

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435
2. Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36(17):1714-1768.
3. Haanen JBAG, et al. Management of toxicities for immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2017;28(Suppl4):i119-i1142.
4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320-341.
5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 1.2022. Published February 28, 2022.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g., infection, progressive disease) – Monitor patients for signs (e.g., tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate Patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography CT scan. – Consider Pulmonary and Infectious Diseases consults
	Grade 1	• No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated.
	Grade 2	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (<10 mg prednisone or equivalent).	**For Grade 2:** – Monitor symptoms daily and consider hospitalization, as clinically indicated. – Consider Pulmonary and Infectious Diseases Consults; – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Consider HRCT or chest CT with contrast, repeat imaging study as clinically indicated.

			– If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with Clinical Study Lead.
	Grade 3 or 4	• Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Hospitalize the patient. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results. – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for *clostridium difficile* toxin, etc.

	defining the CTCAE grade/severity)		– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. - **When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** - **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	• No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management
	Grade 2	• Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Consider further evaluation with imaging study with contrast. – Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

		– If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV prednisone equivalent, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
Grade 3 or 4	**Grade 3** • For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone per day, or equivalent • For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study investigator, in discussion with AstraZeneca Clinical Study Lead. • <u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy, Permanently</u> discontinue both durvalumab and tremelimumab for 1) Grade 3 diarrhea colitis or 2) Any grade of intestinal perforation. **Grade 4**	**For Grade 3 or 4:** – Urgent GI consult and imaging and/or colonoscopy as appropriate. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**

		• Permanently discontinue study drug/study regimen.	
Hepatitis Infliximab should not be used for management of immune-related hepatitis.	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]), and total bilirubin.
PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])	**ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN**	• No dose modifications. • If it worsens, then consider holding therapy.	– Continue transaminase and total bilirubin monitoring per protocol.
	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	• Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT ≥3 × ULN AND bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improving or resolve. – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5 ≤ 10 x ULN	• Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – Perform Hepatology consult, abdominal workup, and imaging as appropriate. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly

	steroid taper (<10 mg prednisone, or equivalent). • If in combination with tremelimumab, do not restart tremelimumab.	start treatment with an additional immunosuppressive (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULNd **ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN**	• Permanently discontinue study drug/study regimen.	- Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. - If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**

Hepatitis (elevated transaminases and total bilirubin) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described:** – Patients should be thoroughly evaluated to rule out any alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate liver function test: AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV)+ patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg). – For hepatitis C (HCV)+ patients: evaluate quantitative HCV viral load – Consider consulting hepatology or Infectious Disease specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml – Consider consulting hepatology or Infectious Disease specialists regarding changing or starting antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with Hepatitis B core antibody (HBcAb) +: Evaluate for both HBV and HCV as above

Isolated AST or ALT > ULN and ≤ 2. 5 x BLV.	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of BILI/Liver decompensation.	
ALT or AST > 2.5 ≤ 5 x BLV and ≤ 20×ULN	• Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5.0 x BLV. • If toxicity worsens then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5.0×BLV, resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist ; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead. – If event is persistent (> 2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

	ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULNd	• Withhold durvalumab and permanently discontinue tremelimumab. • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days.	• Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. • Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. • Consider discussing with Clinical Study Lead, as needed. • If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. • If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. • **Infliximab should NOT be used.**
ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	**Permanently discontinue study drug/study regimen.**		**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider consulting a nephrologist. – Consider imaging studies to rule out any alternative etiology. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria).

grade/severity)	– Follow urine protein/creatinine ratio every 3-7 days.

Grade 1	• No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. – Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated.
Grade 2	• Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2:** – Consider including hydration, electrolyte replacement, and diuretics, as clinically indicated. – Follow urine protein/creatinine ratio every 3-7 days. – Carefully monitor serum creatinine as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out. – If event is persistent beyond 5 days or worsens, increase prednisone up to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol. –
Grade 3 or 4	• Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Follow urine protein/creatinine ratio every 3-7 days. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

			– If event is not responsive within 3 to 5 days of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant.
Rash or Dermatitis (Including Pemphigoid)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID IS CONFIRMED.**
	Grade 1	• No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emolient, lotion, or institutional standard).
	Grade 2	For persistent (>1 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2:** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy. – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**For Grade 3:** • Hold study drug/study regimen until resolution to Grade ≤1 or baseline.	**For Grade 3** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible.

		• If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4:** • Permanently discontinue study drug/study regimen.	**For Grade 4** - Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. - Consider hospitalization. - Monitor the extent of rash [Rule of Nines]. - Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behavior changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g.,

		thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
Grade 1	• No dose modifications.	**For Grade 1:** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2, 3, or 4	• For Grade 2-4 endocrinopathies <u>other than hypothyroidism and Type 1 diabetes mellitus (T1DM),</u> consider holding study drug/study regimen dose until acute symptoms resolve. • Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**.

		investigator or treating physician's clinical judgement.	– For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	**No dose modification**	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** • In consultation with relevant gastroenterology specialist. consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral

	grade/severity)		
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** - Consider IV hydration - Consider Gastroenterology referral
	Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings. If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** • Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Consider Neurology consult. – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (i.e. HSV). – Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal. – Consider IV acyclovir until polymerase chain reactions are available.

Encephalitis	**Any Grade**	• Permanently discontinue study drug/study regimen.	**For Any Grade:** – Consider neurology consult. – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV). – Consider IV acyclovir until polymerase chain reactions are available. – Consider, as necessary, discussing with Clinical Study Lead.(Last bullet). – Consider hospitalization. – Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
	Any Grade **(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	• **General Guidance**	**For Any Grade:** - Consider neurology consult. - Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. - Exclude bacterial and viral infections. (ie HSV). - Consider IV acyclovir until polymerase chain reactions are available. - Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality.
	Grade 2	• Permanently discontinue study drug/study regimen.	**For Grade 2:** – Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisone 1 to 2 mg/kg/day. For progressive symptoms or if oligoclonal bands

			are present consider methylprednisone 1g IV daily for 3-5 days plus IVIG or plasmapheresis.
	Grade 3 or 4	**For Grade 3:** • Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 IV daily for 3-5 days for progressive symptoms. consider adding IVIG or plasmapheresis.
Transverse Myelitis	**Any Grade**	**General Guidance** • Permanently discontinue immunotherapy. • Consider MRI of the spine and brain. • Once imaging is complete, consider lumbar puncture. • Consider testing to rule out additional aetiologies: B12, HIV, rapid plasma regain (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel for anti-Hu and anti-CRMP5/CV2	**For Any Grade:** - **Consider neurology consult** - **Inpatient care** - **Consider prompt initiation of high methylprednisolone pulse dosing** - **Strongly consider IVIG or plasmapheresis**
Peripheral neuropathy	**Any Grade**	**General Guidance**	**For Any Grade:**

(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)		– Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation.
Grade 1	• No dose modifications.	**For Grade 1:** – Consider discussing with the study Clinical Study Lead, as needed. – Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction.
Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2:** – Consult a neurologist. – Consider EMG/NCS – Consider discussing with the Clinical Study Lead, as needed. – Observation for additional sentinel symptoms or consider initiating prednisone 0.5–1 mg/kg orally . – If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
Grade 3 or 4	**For Grade 3 or 4:** • Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider discussing with Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. – Treat per Guillain-Barré Syndrome recommendations.

Guillain-Barré Syndrome (GBS)		**General Guidance**	- Recommend hospitalization - Obtain neurology consult - Obtain MRI of spine to rule out compression lesion - Obtain lumbar puncture - Antibody tests for GBS variants - Pulmonary function tests - Obtain electromyography (EMG) and nerve conduction studies - Frequently monitor pulmonary function tests and neurologic evaluations - Monitor for concurrent autonomic dysfunction - Initiate medication as needed for neuropathic pain
	Grade 2-4	**Grade 2-4** Permanently discontinue	- Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.
Myasthenia gravis		**General Guidance**	- Obtain neurology consult - Recommend hospitalization - Obtain pulmonary function tests - Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies - Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis - Obtain electromyography (EMG) and nerve conduction studies - Consider MRI of brain/spine to rule out CNS involvement by disease - Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)

	Grade 2	**Permanently discontinue**	- Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) - Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	**Permanently discontinue**	- **Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement** - **Start plasmapheresis or IVIG** - **Consider rituximab if refractory to plasmapheresis or IVIG** - **Frequent PFT assessments** - **Daily neurologic evaluations**
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** • Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and

			when to complete a cardiac biopsy, including any other diagnostic procedures. – As indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Consider cardiology consultation and a prompt start of high dose/pulse corticosteroid therapy. – Supportive care (e.g., oxygen). – If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab). IVIG or plasmapheresis or other therapies depending on the clincial condition of the patient, based on the discretion of the treating specialist consultant or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/Polymyositis ("Poly/myositis")	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, and also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD.

		Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the Clinical Study Lead. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
Grade 1	• No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the Clinical Study Lead.
Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV

		equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab). IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3	**For Grade 3:** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 3** – Monitor symptoms closely; recommend hospitalization. - Consider Rheumatology and/or Neurology consult. – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.

1 SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g., immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. • Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	• **For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** • The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** • The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. • Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** • Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines, and society guidelines.

Non–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**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 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	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.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

List of Abbreviations

AChE	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotropic hormone	imAE(s)	Immune-mediated adverse event(s)
ALT	Alanine aminotransferase	INR	International normalized ratio
ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CSP	Clinical Study Protocol	MRCP	Magnetic resonance cholangiopancreatography
CT	Computed tomography	MRI	Magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events	NCCN	National Comprehensive Cancer Network
CTLA-4	Cytotoxic T-Lymphocyte antigen 4	NCI	National Cancer Institute
DILI	Drug-induced liver injury	PD-L1	Programmed cell death ligand-1
ECG	Electrocardiogram	PJP	Pneumocystis jjrovecii pneumonia
ECHO	Echocardiogram	PO	By mouth
ESMO	European Society of Medical Oncology	SCAR	Severe cutaneous adverse reaction
GI	Gastrointestinal	SITC	Society for Immunotherapy of Cancer
HBcAb	Hepatitis B core antibody	SJS	Stephen Johnson Syndrome
HBeAg	Hepatitis B envelope antigen	T1DM	Type 1 diabetes mellitus
HBsAg	Hepatitis B surface antigen	T3	Triiodothyronine
HBV	Hepatitis B virus	T4	Thyroxine
HCC	Hepatocellular cancer	TEN	Toxic Epidermal Necrolysis
HCV	Hepatitis C virus	TMG(s)	Toxicity management guideline(s)
HgA1c	Hemoglobin A1C	TSH	Thyroid stimulating hormone
ICI(s)	Immune checkpoint inhibitor(s)	ULN	Upper limit of normal