A Phase II Study of Olaparib and Durvalumab in Men with Castration Sensitive Biochemically Recurrent Non-Metastatic Prostate Cancer Harboring Mutations in DNA Damage Repair

Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)

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APPROVAL OF PROTOCOL

Title: A Phase II Study of Olaparib and Durvalumab in Men with Castration Sensitive Biochemically Recurrent Non-Metastatic Prostate Cancer Harboring Mutations in DNA Damage Repair

Sponsor Principal Investigator Signature: _____

Print: _____

Date: _____

PCCTC Signature: _____

Print: _____

Date: _____

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Memorial Sloan Kettering Cancer Center (MSKCC) with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles, as adopted by applicable laws and regulations, and to abide by the terms of this protocol.

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

TABLE OF CONTENTS

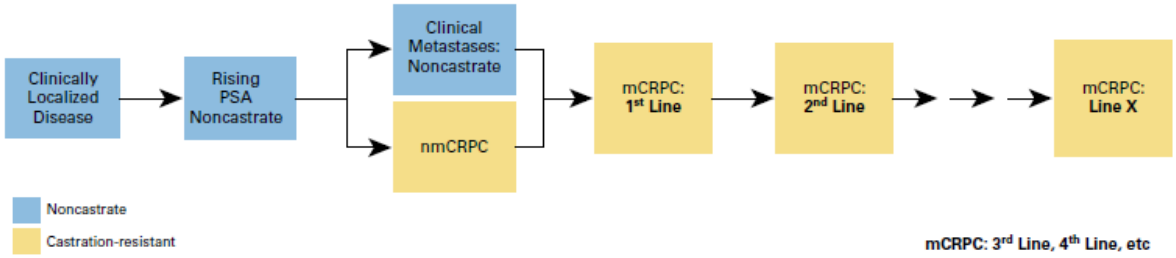
1. INTRODUCTION

1.1 Disease Background

Prostate cancer is the second leading cause of cancer deaths in men. According to American Cancer Society estimates in 2018, as many as 164,690 American men will be diagnosed with prostate cancer, and nearly 29,430 will die of the disease.[1] While many patients may be cured of prostate cancer that is localized to the prostate, others will recur either biochemically (prostate-specific antigen (PSA) progression) consistent with micrometastatic disease, or recur with overt metastatic disease visible on imaging.

The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states (Figure 1). These clinical states involve the complex interplay of a network of signaling molecules that collectively promote net cell proliferation relative to cell death. Based on the extent of disease, hormonal status, and absence or presence of detectable metastases on an imaging study, the states are defined as: localized disease, rising levels of PSA after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate state. Non-castrate prostate cancer refers to a state in which prostate cancer responds to standard hormonal therapy with gonadotropin-releasing hormone (GnRH) analogs (castration sensitive) whereas a castrate state is synonymous with castration resistant disease, wherein cancer progresses despite standard hormonal therapy with GnRH analogs.

Figure 1. Clinical states of prostate cancer[2]



1.2 Background

1.2.1 General background on DNA repair defects

Cancer arises amongst a myriad of genetic alterations resulting in incremental changes in pro-survival or anti-apoptotic pathways. These can arise via germline inheritance or (more commonly) via random somatic genetic events. The DNA repair machinery to counter this implores proteins in direct enzymatic repair, surveillance, regulation of the cell cycle and tertiary organizers of these complex processes.[3] This includes direct DNA repair pathways (Fanconi Anemia pathway, homologous recombination, non-homologous end-joining, base excision repair, direct repair, mismatch repair, nucleotide excision repair, translesion synthesis) and also associated pathways such as cell-cycle checkpoints, ubiquitin response, and chromosomal/chromatin regulation.[4] Loss of these DNA repair pathways results in genomic instability, increased rate of error-prone repair mechanisms and accumulation of non-fatal genomic mutations-the very hallmark of cancer. Disruption of DNA damage repair pathways is observed in many cancers.[5-7] The DNA damage response is broad and requires complex temporal interactions between many proteins. Functional

or expressional loss in these direct and indirect interactions encompasses the DNA damage repair defects.

1.2.2 DNA damage repair mutations are not rare events in prostate cancer

A highlight of what we have learned from the genomic landscape in prostate cancer is the presence of DNA damage repair (DDR) gene mutations and deletions. The Cancer Genome Atlas (TCGA) data in localized prostate cancer found that 19% (62/333) of tumors had a germline or somatic DNA damage repair pathway mutation (BRCA2, BRCA1, CDK12, ATM, FANCD2, and RAD51).[8] Twenty-nine of these cases involved nonsense germline variants and heterozygous deletions without the biallelic inactivation; hence the prevalence may be somewhat lower. In advanced metastatic castration resistant disease using metastatic biopsies, investigators from the Stand Up 2 Cancer – Prostate Cancer Foundation (SU2C-PCF) initiative identified 23% of cases had DNA repair gene alterations.[9] 12.7% of total cases had loss of BRCA2 and 5.6% had mutations in ATM or BRCA1. Thus almost 20% of all mCRPC contain DNA repair defects even when limited to just these three genes. Events were also found with FANCA, PALB2, RAD51B, and RAD51C although at low levels. Hence there is a higher prevalence of DNA Damage Repair (DDR) mutations in more advanced disease; however, a significant number of cases with DDR mutations still exist in earlier clinical states, and are enriched in those with a higher risk of cancer recurrence.

1.2.3 Olaparib (Lynparza) and PARP inhibition

The importance of identifying DDR mutations relates to exploitation of synthetic lethality when PARP inhibitors are used in patients with homologous recombinant repair (HRR) mutations.[10] Poly (ADP ribose) polymerases (PARP) help in the repair of DNA single strand breaks. When PARP 1/2 is inhibited, single strand breaks are not repaired and progress to double strand breaks which are lethal to the cell. Olaparib, a PARP inhibitor, has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.[11-13] Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

Encouraging preclinical data led to study PARP inhibition in BRCA1/2 mutation carriers in clinical trials. The efficacy of olaparib was investigated in a 137-subject subset of a single-arm study with germline BRCA-mutated advanced ovarian cancer and three or more prior lines of chemotherapy. The objective response rate was 34% and the median duration of response was 7.9 months.[14]

Olaparib was ultimately approved in 2014 in advanced ovarian cancer patients who have been treated with three or more lines of chemotherapy.

1.2.4 Clinical experience with Olaparib in prostate cancer

A phase II basket trial which enrolled on the basis of mutation rather than tumor type included men with metastatic castration-resistant prostate cancer (mCRPC).[15] Although it was a small sample, tumor response was seen in half of subjects with prostate cancer, and another 25% with stable disease. Ultimately dedicated trials in prostate cancer were undertaken. PARP inhibition in patients with HRR mutations has led to high response rates

and improved progression-free survival (PFS) in men with CRPC. The responses in a phase II trial with subjects who had refractory CRPC were impressive, with 88% (14/16) clinically benefiting among those harboring a homologous deletion or deleterious mutation in DNA repair genes.[16] Response was a composite endpoint defined as response according to RECIST 1.1, PSA decline > 50%, or conversion in circulating tumor cells (CTCs) from > 5 cells/7.5ml to <5 cells/7.5ml. The maximum PSA declines in those subjects who were considered responders by the composite definition ranged from no PSA decline to 95% decline. 11/16 responders had a PSA decline of > 50%.

The success seen with PARP inhibition in select populations with DNA damage repair mutations in prostate cancer has led to fast track approval with the US FDA for olaparib. The PROFOUND trial, a phase III trial of olaparib compared to oncologist treatment choice in DDR mutated subjects (NCT02987543) has resulted and led to the FDA approval for metastatic castration resistant prostate cancer.[17] The trial enrolled men with mutations in DNA repair genes and divided them into two cohorts. Cohort A included men with alterations in the *BRCA1*, *BRCA2*, or *ATM* genes, each of which plays an important role in DNA repair. Cohort B included men who had alterations in a group of 12 other genes that have some involvement in repairing DNA. Based on improvements in overall survival of approximately 4 months, Olaparib was FDA approved for men with DDRs alterations.

From the mature ovarian and breast cancer trial experience in subjects harboring a BRCA mutation, it is recognized that resistance develops and hence combination trials and methods of re-sensitizing or enhancing durability are essential.[18,19] Additionally, maintenance therapy with olaparib adds benefit as seen in the ovarian population.[20]

1.2.5 Toxicity experience

A full description of the emerging safety profile for olaparib, with guidance for investigators, is provided in the IB.

This section lists those adverse events (AEs) and laboratory abnormalities experienced in ≥20% subjects that are currently regarded as expected for regulatory reporting purposes.

- Hematological toxicity, generally low grade (CTCAE Grade 1 or 2):
  - Anemia

- Non-hematological toxicity, generally mild or moderate (CTCAE Grade 1 or 2), intermittent and manageable on continued treatment:
  - Nausea
  - Fatigue
  - Vomiting
  - Diarrhea
  - Decreased appetite

CTCAE = NCI Common Terminology Criteria for Adverse Events

1.2.6 PD(L) 1 as a target to treat cancer

It is known that cancers can be recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors.[21] PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor[22] and to CD80.[23] PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFNγ) and can be found on both tumor cells and tumor-infiltrating immune cells. The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target tumor cells and protecting the tumor from immune elimination.[24] PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not fully elucidated.[23,25]

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, anti–PD-L1 antibodies have been used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients.[26-31] This has led to FDA approval of anti PD(L)1 antibodies in multiple malignancies including melanoma, NSCLC, squamous head and neck cancer, kidney cancer, urothelial cancer, and mismatch repair protein deficient patients irrespective of tumor origin.[32,33]

1.2.7 Durvalumab

Durvalumab is a 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.[34] In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism.[34] 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 9000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents, and is FDA approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who either have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum- containing chemotherapy. Approval was based on one single-arm trial of 182 subjects with locally advanced or metastatic urothelial carcinoma whose disease progressed after prior platinum-containing chemotherapy (NCT01693562).[35,36] Durvalumab, 10 mg/kg intravenously, was administered every 2 weeks. Confirmed objective response rate (ORR) as assessed by blinded independent central review per RECIST 1.1, was 17.0% (95% CI: 11.9, 23.3). At the data cutoff for the ORR analysis, median response duration was not reached (range: 0.9+ to 19.9+ months). ORR was also analyzed by PD-L1 expression status as measured by VENTANA PD-L1 (SP263) Assay. In the 182 subjects, the confirmed ORR was 26% (26% CI: 17.8, 36.4) in 95 subjects with a high PD-L1 score and 4% (4% CI: 0.9, 11.5) in 73 subjects with a low or negative PD-L1 score.[36]

Toxicity from Treatment with Durvalumab

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

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

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of subjects) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of subjects experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of subjects experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics. The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure.

Rationale for 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 subjects 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.[37-40] 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.[38] 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.[39]

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, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

1.2.8 PD(L)1 therapy in prostate cancer

Emerging data with pembrolizumab (anti-PD1 antibody) in mCRPC has also shown recent promise to a field previously lagging behind other genitourinary malignancies with approved anti-PD(L)1 options such as bladder and renal cell carcinoma; checkpoint blockade with ipilimumab produced disappointing results in the pre- and post-chemotherapy CRPC setting, and there was little therapeutic study of the PD1 pathway in prostate cancer after a phase I trial published in 2012 of nivolumab did not identify any complete or partial responses in 17 subjects with advanced CRPC.[30,41,42] More recently, however, Graff et al (2016) evaluated the benefit of adding pembrolizumab to enzalutamide (an androgen receptor (AR) antagonist approved in mCRPC) in subjects who were progressing (after initial response) on enzalutamide; 5/27 subjects have responded as measured by dramatic PSA declines and reductions in tumor burden on computerized tomography (CT) scan.[43] Of the published data which reported the first 10 subjects (with 3 responders), the 3 PSA nadirs in those subjects benefiting from treatment were 0.08, 0.02, <0.01. One of these subjects had mismatch repair protein deficiency, which is known from the colorectal experience and other published trials to be associated with a much

higher likelihood of responding to PD1 blockade, suspected as a result of higher mutational loads and subsequent neoantigen presentation.[44,45] The FDA has approved pembrolizumab across all refractory metastatic solid tumors who harbor deficiency in mismatch repair, though very few subjects with prostate cancer were part of this analysis. Mismatch repair protein deficiency occurs in approximately 2-5% of metastatic prostate cancer.[46]

1.2.9 Combination PARP inhibition and anti-PD(L)1 therapy

Using PARP inhibition to treat tumors deficient in homologous recombinant repair can reduce tumor burden and incite apoptosis with demonstrable clinical benefit. Preclinically, PARP inhibition is associated with triggering the cyclic GMP-AMP synthase (cGAS)-Stimulator of Interferon Genes (STING) pathway, and upregulation of PD-L1.[47] However, this has not been evaluated in any prospective clinical trials. Additionally, BRCA2 loss leads to greater genomic instability, which is associated with neo-epitope formation and potential increased sensitivity to checkpoint blockade. A natural extension of these findings is to combine PARP inhibition with an anti-PD-L1 antibody.

The combination of PARP inhibition and anti PD(L)1 antibodies is being explored in several malignancies including NSCLC (NCT03308942), triple negative breast cancer and ovarian cancer (NCT02657889; NCT02484404). It is also being investigated in mCRPC (NCT02657889). A trial being conducted at the NCI evaluating durvalumab with olaparib (NCT02484404) with a cohort of subjects with metastatic CRPC in an unselected population (did not require the presence of DDR) suggests a manageable safety profile and early but promising results. As presented at ASCO 2017, seven (of 16) subjects (44%) on-study >2 months have had PSA declines > 50%.[48]

1.2.10 Options for patients with biochemical recurrence

For men with biochemically recurrent, non-metastatic prostate cancer, options for management include observation, initiation of androgen deprivation therapy (ADT), salvage radiation therapy, or participation in clinical trials. The decision to initiate therapy is dependent upon multiple factors including PSA, PSA doubling time (as a reflection of risk of development of metastatic disease), patient comorbidities and preferences, as well as clinician preferences.

Most of the ADT therapies approved for prostate cancer have been on the basis of an equivalent effect on serum testosterone levels, or an improved safety profile relative to other available agents.[49-51] None have shown superiority in a cancer specific outcome such as an improvement in disease related symptoms, time to progression or overall survival. A Canadian study comparing intermittent versus continuous ADT in non-metastatic biochemically recurrent prostate cancer showed no difference in cancer specific outcomes, but an improvement in prostate cancer and therapy related adverse events for men treated on the intermittent approach.[52] With an intermittent approach, men receive ADT for a fixed period of time in which PSA declines, then ADT is intentionally held and not restarted until the PSA again begins to rise. Many have explored the approach with “on cycles” of varied duration, but in most studies, the maximal response is observed by 8 months of ADT, and 6-9 months is standard.[53] Castrate levels of testosterone can be achieved within 48-72 hours with the administration of a GnRH

antagonist, degarelix. ADT has been shown to induce apoptosis of prostate cancer cells;[54] potentially leading to the release of tumor antigens.

Although ADT serves as the primary basis of treatment in recurrent non-castrate (castration sensitive) biochemically recurrent prostate cancer that is at risk of metastatic recurrence, lowering testosterone to castrate levels comes with significant quality of life disturbance to men; this includes decreased libido, erectile dysfunction, fatigue, muscle loss, weight gain, hot flashes, bone density loss, and potentially increased risk of cardiovascular events, cognitive impairment, and diabetes.[55-57] As a consequence, many patients at risk for developing lethal forms of the disease are appropriately interested in alternatives to ADT, in hopes of avoiding ADT toxicities and preventing or delaying CRPC.

1.3 Rationale

Therapy for recurrent prostate cancer has a long history of hormonal manipulation which led to advances with second generation AR-directed agents such as enzalutamide in CRPC; however, molecular profiling and immuno-oncology is revolutionizing the field and bringing new pathways to the forefront with potential to transform the management and natural history of this disease yet again. In this proposed trial for men with castration sensitive disease, we will exploit synthetic lethality using PARP inhibition (olaparib) in those subjects with somatic and germline DNA damage repair (DDR) mutations, and couple this with anti-PDL1 immunotherapy (durvalumab) for enhanced and durable effect. We will first explore the combination without ADT, as a regimen that can avoid the quality of life detriment associated with ADT, which would be a milestone for the field if successful. For those who do not fully respond with olaparib and durvalumab alone, ADT will be added for a fixed course to potentially salvage with triplet therapy.

1.3.1 Rationale for trial endpoint and population

The primary endpoint of this trial offers a clear signal of efficacy as an undetectable PSA with non-castrate levels of testosterone at 24 months suggests no malignant tumor cells are producing PSA and hence are not active. This has been used in other clinical trials (NCT02020070; NCT01751451) and offers an advantage over other interim endpoints such as PSA progression, radiographic PFS (e.g., time to metastatic disease), development of CRPC, or OS which can require a very lengthy follow up period in castration sensitive disease. An undetectable PSA in a subject who is post prostatectomy is a clear sign of the absence of cancer activity. Durability of an undetectable PSA in an environment rich with testosterone is synonymous with cure, and analogous to a complete response in solid tumors. Secondary endpoints, more synonymous with progression free survival (PFS) used in other immunotherapy trials, will also be collected and informative of the efficacy of this regimen.

This trial will include men who have had a radical prostatectomy and/or primary definitive radiation therapy to the prostate and have developed biochemical non-metastatic recurrence with a PSA doubling time placing them at high risk for metastases. This trial will allow those subjects who are ADT naïve, as well as those who have received intermittent ADT and currently are on an 'off cycle' of ADT. Allowance of subjects who have received a prior cycle of ADT and failed allows them to serve as their own control. In the biochemically recurrent "non-metastatic" population, the inability to identify gross metastatic disease is more a function of the limitations of conventional imaging (CT and

technicium bone scan) than it is a reflection of not having micro-metastatic recurrence. As novel tracers such as Prostate Specific Membrane Antigen (PSMA) PET imaging identifies disease earlier, and with greater sensitivity, a lead time bias is anticipated across trials. With more sensitive imaging, subjects with earlier metastatic disease may be enrolled in metastatic trials in the future. This trial will use conventional imaging with CT/MRI and bone scan to define non-metastatic disease. It will not exclude those subjects with disease only detectable using investigational PET imaging.

Moving into earlier disease states in the prostate cancer continuum is appealing as the immune system may be more receptive with fewer immunosuppressive cells and with less tumor burden to overcome. In clinical trials with prostate cancer, there have been hints that lower disease burden may be a more optimal setting for immunotherapy. Post hoc analysis of the IMPACT trial which evaluated the sipuleucel-T vaccine in mCRPC demonstrated that the subset of subjects with PSA values in the lowest quartile were more likely to benefit than those with PSA (as a very loose reflection of burden) in the highest quartile.[58] More recent data in melanoma using anti-PD1 antibodies suggests the ratio of reinvigorated exhausted T cells relative to tumor burden can be predictive of response to anti-PD1 therapy. The authors postulated that if the tumor burden is high, even a robust reinvigoration of T cells may not be enough.[59]

Outside of the hypotheses generated for the timing of immunotherapy, there is growing evidence that utilization of chemotherapy, and more potent anti-androgens such as abiraterone previously only used in the castration resistant setting can have a more profound impact when used in castration sensitive disease relative to ADT alone. The use of ADT with docetaxel for 6 cycles in metastatic castration sensitive prostate cancer as compared to ADT alone as well as abiraterone with prednisone with ADT relative to ADT alone in the castration sensitive (non-castrate) metastatic disease setting are now supported by several large phase III trials [60] The CHAARTED trial found the greatest benefit in those deemed to have a higher 'burden' of metastatic disease and the LATITUDE trial required at least 3 bone metastases.[60-62] Where subjects with minimal metastatic disease (e.g., 1-2 bone metastases, or low volume unresectable nodal disease) are best served is not altogether clear.

1.3.2 Hypothesis

PARP inhibition in subjects with prostate cancer harboring HRR mutations will reduce tumor burden and cause apoptosis of the cell, leading to neoantigen release, activation of the cyclic GMP-AMP synthase (cGAS)-Stimulator of Interferon Genes (STING) pathway, which in combination with PDL1 blockade may lead to durable responses. This combination may be effective in treating recurrent prostate cancer without the use of ADT, a maneuver which is associated with only temporary response, an inability to cure, and significant quality of life detriment. For those who do not achieve an undetectable PSA with normal testosterone at 4 months, ADT for a fixed course will be added starting the following cycle to determine if they can be "salvaged" with triplet therapy, as ADT has been demonstrated to increase cytotoxic T cell proliferation and will reduce tumor burden.

2. OBJECTIVES

2.1 Primary Objective

To assess the therapeutic efficacy as defined by an undetectable PSA (<0.05 or PSA <0.10 for institutions where this is the lower limit of detection) with non-castrate levels of testosterone using the combination olaparib (PARP inhibition) with durvalumab (PDL1 inhibition) at 24 months (cycle 24) in biochemically recurrent prostate cancer.

2.2 Secondary Objectives

- To determine if a non-castrating regimen can provide disease control as measured by an undetectable PSA (without ADT) at 5 months (cycle 5).
- To evaluate the safety of the combination of olaparib and durvalumab

2.3 Exploratory Objectives

To determine:

- Undetectable PSA at 11 months (cycle 11) (irrespective of testosterone level)
- Time to PSA progression defined as the time to PSA increase that is ≥ 25% and ≥ 2ng/mL above the nadir, and which is confirmed by a second value > 3 weeks later
- Change in PSA doubling time at 24 months relative to PSA doubling time from the first dose of study drug (using the last 3 values from each time point)
- Comparison of Patient Reported Outcome (PRO) assessments of toxicity (PRO-CTCAE) to clinician reported toxicity assessments (CTCAE v.5.0)
- Changes in immune biomarkers with treatment. Peripheral blood mononuclear cells (PBMCs) will be collected that can later be analyzed for the immunomodulatory effects of the regimen by measuring for example, discrete T-cell populations. Archival tissue will also be analyzed for immune-related genes that may associate with response.

3. SUBJECT SELECTION

3.1 Inclusion Criteria

To be included in this study, subjects should complete all screening procedures and meet all of the following criteria:

3.1.1 Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information. A signed informed consent must be obtained before screening procedures are performed.

NOTE: HIPAA authorization may be either included in the informed consent or obtained separately.

3.1.2 Males 18 years of age and above

3.1.3 Body weight > 30kg

3.1.4 History of radical prostatectomy and/or primary radiation therapy to the prostate

3.1.5 Histologically confirmed prostate cancer with progressive disease defined as:

- Rising PSA (50% or more increase to a level of 0.50 ng/mL or more, based on at least 3 PSA determinations obtained at least 1 week apart). The 50% rise in PSA is across the 3 determinations, and these determinations do not need to be sequential.
- PSA doubling time of ≤ 9months as calculated according to the Memorial Sloan Kettering Cancer Center nomogram (http://www.mskcc.org/mskcc/html/10088.cfm)

3.1.6 No evidence of metastatic disease on conventional imaging (CT/MRI and bone scan). However, subjects with pelvic and/or retroperitoneal nodes < 2cm in the short axis will be permitted on study, as they are considered not to have definitive metastases. *(Note: Metastatic disease on investigational imaging, Prostate Specific Membrane Antigen-targeted (PSMA) PET, PET-choline, or other novel PET tracers who do not have evidence of metastatic disease using conventional imaging (CT/MRI, bone scan) are allowed.)*

3.1.7 Molecular evidence of DDR deleterious mutations (somatic or germline), including BRCA1, BRCA2, ATM, CHEK1, CHEK2, FANCA, RAD51B, RAD51C, RAD51D, RAD54L, PALB2, BRIP1, BARD1, or CDK12. Mutations may be truncating, splice site mutations, missense or homozygous deletions. Mutation status is determined by a local laboratory with the result documented in the subject's medical record, previously obtained genomic testing from a CLIA-certified lab, or via archival or fresh tissue.

3.1.8 ECOG status of ≤ 1 (Appendix A: Performance Status Criteria)

3.1.9 Normal organ function with acceptable initial laboratory values within 14 days of treatment start:

WBC	³ 2000/µl
ANC	³ 1500/µL
Hemoglobin	³ 10g/dL
Platelet count	³ 100,000/µl
Creatinine Clearance	≥51 mL/min estimated using the Cockcroft-Gault equation Estimated creatinine Clearance = (140-age [years]) x weight (kg) / serum creatinine (mg/dL) x 72
Bilirubin	≤ 1.5 ULN (unless documented Gilbert's disease)
SGOT (AST)	£ 2.5 x ULN (unless liver metastases are present, in which case AST must be £ 5 x ULN)
SGPT (ALT)	£ 2.5 x ULN (unless liver metastases are present, in which case ALT must be £ 5 x ULN)

3.1.10 Non-castrate level of testosterone defined as a value ³ 150 ng/dL

3.1.10 Life expectancy of ≥ 52 weeks.

3.1.11 Agree to use two medically acceptable, highly effective forms of birth control (e.g., spermicide in conjunction with a barrier such as a condom) or sexual abstinence for the duration of the study, including 180 days after the last dose of study drug. Sperm donation is prohibited during the study and for 3 months after the last dose of study drug.

Female partners of childbearing potential should use hormonal or barrier contraception unless postmenopausal or abstinent.

3.2 Exclusion Criteria

3.2.1 No other malignancy from which the subject has been disease-free for less than 3 years, with the exception of adequately treated and cured non-invasive malignancies such as basal or squamous cell skin cancer or superficial bladder cancer.

3.2.2 Less than one month prior to treatment start from last prior regimen or radiation exposure. Prior radiotherapy to the prostate (adjuvant or salvage radiotherapy) is allowed.

3.2.3 No prior investigational use with an anti-PD(1) including durvalumab or anti-CTLA4 antibody.

3.2.4 No prior treatment with a PARP inhibitor, including olaparib.

3.2.5 No concomitant or prior therapy with any of the following: IL-2, interferon, or other non-study immunotherapy regimens; immunosuppressive agents; or chronic use of systemic corticosteroids within 6 weeks of treatment start. Exceptions include: 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)

3.2.6 No receipt of live attenuated vaccine within 30 days prior to treatment start *Note: enrolled subjects should not receive live vaccine while receiving IP and up to 30 days after the last dose of study therapy*

3.2.7 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 treatment start is 2 weeks.

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

3.2.9 More than 2 cycles of intermittent hormones for the treatment of biochemical recurrence, with a cycle defined as a period of consistent ADT (generally 3-12 months) followed by intentional cessation of ADT without re-initiation of ADT until the PSA rises. Prior ADT in the treatment of localized prostate cancer or with salvage radiation therapy is allowed. Prior use of abiraterone acetate with prednisone, enzalutamide, apalutamide, or other androgen receptor/androgen biosynthesis inhibitors are allowed if used in the localized or biochemically recurrent disease state provided that there was no evidence of disease progression while on these therapies.

3.2.10 No medical conditions such as uncontrolled hypertension, uncontrolled diabetes mellitus, cardiac disease that would, in the opinion of the investigator, make this protocol unreasonably hazardous.

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

3.2.12 No active infection including tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or active infection with human immunodeficiency virus (positive HIV 1/2 antibodies). Subjects with a past or resolved HBV infection (defined as presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA

3.2.13 No autoimmune disease: subjects with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are subjects with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Sarcoidosis syndrome or Wegener's granulomatosis with polyangiitis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre syndrome and myasthenia gravis); Graves' disease. Exceptions include history of eczema, vitiligo, alopecia, hypothyroidism (e.g., following Hashimoto syndrome), and any chronic skin condition that does not require systemic therapy; subjects without active disease in the last 5 years prior to treatment start may be included but only after consultation with the treating physician. Exceptions may be made on a case by case basis upon discussion with the Sponsor Principal Investigator.

3.2.14 No history of active primary immunodeficiency

3.2.15 No major surgery within 4 weeks of treatment start. Subjects must have recovered from any significant effects of any major surgery but investigators may discuss with the Sponsor Principal Investigator in the case of any exceptions.

3.2.16 No blood transfusion within 28 days of treatment start.

3.2.17 Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome

3.2.18 Enrollment in another clinical trial with a therapeutic agent. Subjects may co-enroll on investigational imaging studies (e.g., PSMA PET) or correlative trials.

3.2.19 No previous allogeneic bone marrow transplant or double umbilical cord blood transplant.

3.2.20 No history of leptomeningeal carcinomatosis

3.2.21 No unresolved toxicity (Common Terminology Criteria for Adverse Event (CTCAE) Grade ≥ 2) caused by previous anticancer therapy, excluding alopecia, vitiligo, and the laboratory values described in the inclusion criteria. Subjects with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Sponsor Principal Investigator. Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with study drugs may be included only after consultation with the Sponsor Principal Investigator.

3.2.22 No subjects who are HIV-positive on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with olaparib. In addition, these subjects are at increased risk of lethal infections when treated with marrow suppressive therapy.

3.2.23 No subjects with baseline moderate to severe hepatic impairment (Child-Pugh Class B and C).

3.2.24 No subjects with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

3.2.25 No known allergy to any of the compounds under investigation or excipients of the product.

3.2.26 Subjects unable to swallow orally administered medication and subjects with gastrointestinal disorders likely to interfere with absorption of the study medication.

3.2.27 No other condition which, in the opinion of the investigator, would preclude participation in this trial.

4. ENROLLMENT PLAN

4.1 Enrollment Plan

4.1.1 Anticipated Enrollment

This study is anticipated to enroll 32 subjects.

4.1.2 Recruitment

Potential research subjects will be identified by a member of the subject's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Urology offices. Investigators will screen the subject's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study.

4.2 Eligibility Confirmation

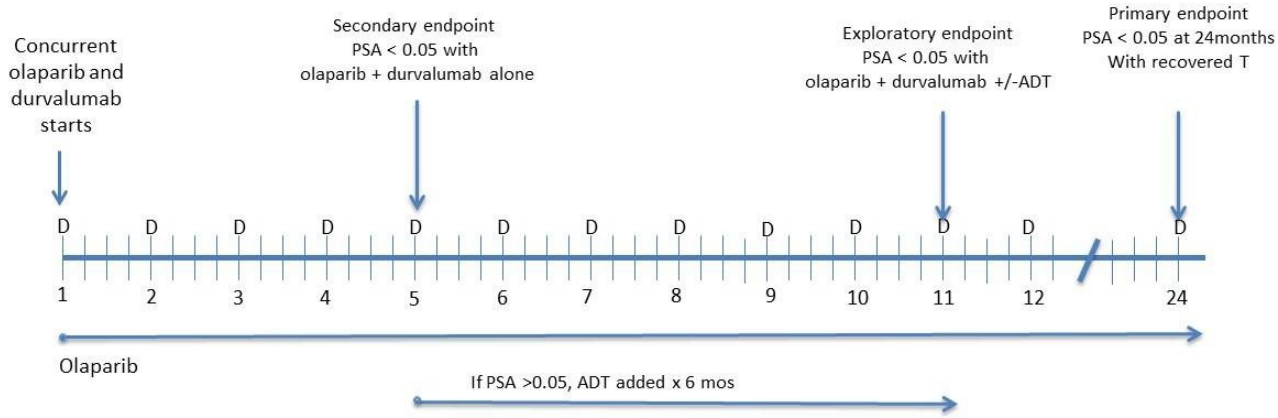
Confirmation of eligibility will be completed centrally by the PCCTC prior to treatment start. A record of subjects who fail to meet eligibility criteria (i.e., screen failures) will be maintained. A complete, signed informed consent and HIPAA authorization are required as part of eligibility confirmation. All subjects must sign an IRB-approved informed consent prior to starting any protocol-specific procedures; however, evaluations performed as part of routine care prior to informed consent can be used for screening and eligibility confirmation.

5. TREATMENT/INTERVENTION PLAN

This is a phase II, single arm, multi-center trial that will evaluate the combination of olaparib 300mg twice daily (600mg total daily dose) with durvalumab 1500mg IV monthly in biochemically recurrent castration sensitive prostate cancer. The trial will be conducted at sites who are members of the PCCTC Network.

As seen in the trial design (Figure 2), subjects will be treated concurrently with olaparib + durvalumab continuously for 24 months. After the first 4 months, if a subject fails to achieve an undetectable PSA with the combination of olaparib and durvalumab, ADT will be added for 6 months (starting at Cycle 5) while continuing treatment with olaparib and durvalumab. For subjects who have an undetectable PSA [PSA of <0.05 or PSA <0.10) for institutions where this is the lower limit of detection] after the first 4 months of treatment, they will continue on the combination of olaparib + durvalumab continuously for 24 months (without ADT). As long as it is believed that subjects are clinically benefiting, they will remain on treatment for up to 24 months with olaparib and durvalumab. For example, a subject with a PSA reduction that does not achieve an undetectable PSA would be allowed to remain on study for the duration of the trial. Subjects who meet progression criteria while on active therapy would come off of trial. If subjects respond and later progress in the one-year follow-up period (beyond 24 months), they will be allowed to be re-induced with the combination.

Figure 2. Study schema for olaparib and durvalumab in subjects with castration-sensitive prostate cancer (biochemical recurrence) harboring DNA damage repair mutations



DDR deleterious mutations (somatic or germline) will include BRCA1 (breast cancer susceptibility gene), BRCA2, ATM (ataxia telangiectasia mutated serine/threonine kinase), CHEK2, FANCA, RAD51C, RAD51D, PALB2, BRIP1, BARD1, and CDK12. Mutations may be truncating, splice site mutations, missense or homozygous deletions. Subjects will be allowed on trial using local testing, previously obtained genomic testing from a validated lab (e.g., expedited germline testing from Color), or via archival or fresh tissue.

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Appendix B.

5.1 Study Procedures

5.1.1 Informed consent and research/HIPAA authorization

Before initiating any protocol-specific screening activities, the scope of the study should be explained to each subject. Subjects should be consented in accordance with Section 11.3 Written Informed Consent, including completion of a research/HIPAA authorization.

5.1.2 Inclusion/exclusion criteria

During the screening period, subject eligibility will be determined according to the inclusion and exclusion criteria (Sections 3.1 Inclusion Criteria & 3.2 Exclusion Criteria).

5.1.3 Demographics and medical history

Demographics and medical history collected will include:

- Date of birth (or age if date of birth is not allowed to be collected by local regulations)
- Significant past and ongoing conditions
- Dates of the primary prostatectomy and pathologic state
- Dates of prior radiation therapy
- Dates of prior hormonal therapies

5.1.4 Concomitant medications

Concomitant medications are permitted while on study if the medication is not expected to interfere with the evaluation of safety or efficacy, and is not otherwise restricted or prohibited (see Appendix C for a listing of medications with the potential for drug interactions).

5.1.5 Vital signs, height, and weight

Vitals will include temperature, blood pressure, and pulse. Height and weight will also be collected as described in Appendix B.

5.1.6 Performance Status

Performance status will be assessed using ECOG or Karnofsky scales (Appendix A).

5.1.7 Physical examination

A complete physical examination will be performed at screening. A symptom-directed physical exam may be performed at subsequent visits.

5.1.8 Histologic and radiologic (per PCWG3 and RECIST 1.1 criteria) confirmation of disease

Pathologic confirmation of prostate cancer and no evidence of metastasis on conventional CT or Bone Scan.

5.1.9 Laboratory tests

Laboratory tests will be performed by local labs and will include:

- CBC with differential: white blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes (LYMP), monocytes (MONP), eosinophils (EOSP), basophils (BASOP)). If absolute differentials not available please provide % differentials.

- PSA
- Serum testosterone (TEST)
- Comprehensive Metabolic Panel (CMP): glucose (GLU), calcium (CA), albumin (ALB), total protein (TP), sodium (NA), potassium (K), bicarbonate (CO2), chloride (CL), blood urea nitrogen (BUN), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI)
- Thyroid function tests: TSH, free T4 and free T3
- Urinalysis: pH, specific gravity, hemoglobin, glucose, ketones, and protein by dipstick, with microscopic exam if any of the dipstick analytes are 2+ or higher.
- Coagulation Tests: Coagulation [activated partial thromboblastin time (APTT) and international normalized ratio (INR)] will be performed at baseline and if clinically indicated unless the subject is receiving warfarin. Subjects taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. The reason(s) for the use, doses and dates of treatment should be recorded in the subject's medical records and appropriate section of the EDC.
- If clinically indicated, the investigator may order amylase and lipase
- Bone marrow or blood cytogenetic samples may be collected for subjects with prolonged hematological toxicities

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

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

In case a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN please refer to Appendix C: 'Actions required in cases of combined increase of aminotransferase and Total Bilirubin – Hy's Law', for further instructions

5.1.10 ECG

All ECGs should be 12-lead ECGs performed in a supine position. ECGs should be performed prior to drawing blood when possible. An ECG is required prior to starting study treatment and when clinically indicated.

Twelve-lead ECGs will be obtained after the subject has been rested in a supine position for at least 5 minutes in each case. ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the site will record it as an AE on the eCRF. The original ECG traces must be stored in the subject medical record as source data.

5.1.11 Computerized tomography (CT) or magnetic resonance imaging (MRI)
Radiographic evaluations will include CT of the chest, abdomen, and pelvis with contrast or MRI with contrast of the abdomen and pelvis, and CT chest without contrast. The method of assessment and techniques while on study should be the same as used at baseline.

5.1.12 Radionuclide bone scan
Radionuclide bone scanning (whole body) should be performed using 99mTc-methylene.

5.1.13 Select PRO – CTCAE
Designed to assess potential drug toxicity from the patient perspective (Appendix F)

5.2 Correlative/Special Studies

5.2.1 Blood Biomarkers: PBMCs and serum will be collected while on trial for future investigation of immune correlatives. This may include evaluation of T-cell subsets and immunophenotyping, functional status of T effector cells, multiplex cytokine analysis, tumor associated antigens; cfDNA will also be collected for potential future use.

5.2.3 PDL-1 Expression: PDL-1 expression may be performed in the future using archival prostatectomy or prostate biopsy tissue.

5.2.4 Next generation sequencing and analysis of mutational load, immune driver genes, activation of the cyclic GMP-AMP synthase (cGAS)-Stimulator of Interferon Genes (STING) pathway, and immune microenvironment characterization may be performed using archived prostatectomy or prostate biopsy tissue.

5.2.5 As part of eligibility to determine if a subject has a DNA Damage Repair alteration, a matched normal control sample (e.g., blood or saliva) may be required dependent upon the assay being utilized. MSK-IMPACT requires a normal control blood sample while Tempus uses a saliva sample.

5.3 Follow-up (Every 12 weeks)

Subjects will be followed per the schedule in Appendix B. Subjects withdrawn from the study because of AEs will be followed until the adverse event has either resolved or stabilized. Reasons for premature withdrawal should be determined and noted.

5.4 Dose Modifications

If subject requires that the study drug be discontinued because of an adverse event (as described below) or have a treatment interruption of greater than 8 weeks for olaparib or 8 weeks for durvalumab, at the investigator's discretion, they may continue on the other agent alone until progression. Refer to Appendix G and Appendix H for management of toxicities.

5.4.1 Durvalumab Dose Modification
Dose reductions for durvalumab are not permitted. For dose modification and toxicity management guidelines for durvalumab, refer to Appendix G.

5.4.2 Olaparib dose levels

Dose Level	Olaparib
Level 0	300 mg BID
Level -1	250 mg BID
Level -2	200 mg BID
Level -3	Discontinue

Subjects requiring more than two dose reductions will have to discontinue olaparib. 100 mg and 150 mg tablets will be supplied for olaparib.

5.4.3 Toxicities that require discontinuation from study treatment
Protocol therapy should be discontinued if a subject experiences:

- Any CTCAE Grade 4 toxicity with the exception of:
  - CTCAE Grade 4 neutropenia of 5 days or fewer duration
  - CTCAE Grade 4 nausea/vomiting or diarrhea that resolves to Grade 3 or less within 72 hours
  - CTCAE Grade 4 laboratory abnormalities that can be readily corrected with 72 hours and do not result in hospitalization.
- CTCAE Grade 3 thrombocytopenia with hemorrhage
- CTCAE Grade 3 febrile neutropenia
- Hy's Law (AST or ALT >3x ULN with concomitant serum bilirubin >2x ULN and no alternate etiology)
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)

5.5 Concomitant Medications and Supportive Care

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented on the eCRF.

Subjects should not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab or olaparib.

Refer to Appendix D for more information on concomitant medications and supportive care guidance.

5.6 Other Concomitant Treatment

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

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

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

5.7 Removing Subjects from the Protocol

In the absence of treatment delays because of adverse events, treatment will continue for 24 cycles or until one of the following criteria applies:

- Withdrawal by subject: subject decides to withdraw from the study
- Progressive disease. PSA progression during the treatment period is defined as a rising PSA confirmed on repeat measurement at least two weeks later and at a least 25% rise and 2 ng/mL above nadir or baseline, whichever is lower. The assessment for PSA progression that may lead to discontinuation while on treatment will not begin prior to Cycle 6 as ADT would not start until Cycle 5. PSA progression during the follow up period defined as PSA > 0.2 ng/mL confirmed by repeat measurement at least 2 weeks later.
- symptomatic disease progression at any time
- objective clinical disease progression
- Intercurrent illness that prevents further administration of treatment, including bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Adverse event: unacceptable adverse event(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the subject to be retreated
- Physician decision: general or specific changes in the subject's condition that render the subject unacceptable for further treatment, in the judgment of the investigator

Because an excessive rate of withdrawals can render the study uninterpretable, unnecessary withdrawal of subjects should be avoided. When a subject discontinues treatment early, the investigator should make every effort to contact the subject and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

6. THERAPEUTIC AGENTS

6.1 **Durvalumab** (MEDI4736)

Description

Durvalumab is a human mAb of the 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).

Pharmacokinetics

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

Dosage Selected, Preparation, and Schedule of Administration

Subjects will receive 1500mg durvalumab (MEDI4736) on Day 1 of each cycle via IV infusion every 4 weeks. 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

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 1500 mg (for subjects >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 (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (i.e., 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing (for subjects ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Do not co-administer other drugs through the same infusion line.

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

In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Durvalumab will be administered at room temperature (approximately 20-25°C) by controlled infusion into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes). Less than 55 minutes is considered a deviation, the total allowed time should not exceed 8 hours at room temperature.

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.

<u>Monitoring of dose administration</u>
Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). Subjects will be monitored before, during and after the infusion with assessment of vital signs at the following times. Subjects

are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). First infusion: On the first infusion day, subjects will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IP. BP and pulse will be collected from subjects 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. Subsequent infusions: BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Subjects 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.

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 subjects 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, with maximum total time at room temperature not exceeding 8 hours (otherwise requires new infusion preparation). For management of subjects who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix G.

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 subjects to an intensive care unit if necessary.

Supply and packaging

Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration.

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL.

Storage requirements

All study drugs should be kept in a secure place under appropriate storage conditions. Drug product should be kept in original secondary packaging until use to prevent prolonged exposure

to light. The investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage.

Durvalumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

For more information refer to the current version of the durvalumab IB.

6.2 Olaparib (AZD2281, KU-0059436) (NSC#: 747856)

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

Molecular Formula
$C_{24}H_{23}FN_4O_3$

Molecular Weight
434 Daltons

Supply and Packaging
The Astra-Zeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to the site. Olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain 32 tablets and desiccant. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose. Bottles will be labeled per local regulations.

Drug product Administration
Two 150mg tablets orally twice daily with or without food (600 mg total daily dose). The tablets are to be swallowed whole with water. Tablets cannot be broken, opened, or chewed.

Olaparib will be dispensed to subjects on Day 1 and every 28 days thereafter until the subject completes the study, withdraws from the study or closure of the study.

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

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 subject 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 subject 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 subject should take their allotted dose at the next scheduled time.

There are no special dosing instructions for olaparib on days when durvalumab is administered.

Labeling
Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. 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.

The label will include the following information:

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

Storage Requirements
All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the IB specifies the appropriate storage.

Subjects will continue treatment until disease progression, unacceptable toxicity or other reason for discontinuation of protocol treatment (Section 5.6).

Intake Calendar: Olaparib compliance will be recorded on an Intake Calendar/Pill Diary. Institutional staff will review and ascertain subject adherence with protocol treatment. If a dose is missed, subjects are to take the normal dose on the following day. If more than one daily dose is missed, the study doctor or study team must be informed.

Pharmacokinetics

Absorption
Following oral administration of olaparib via the capsule formulation, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple dosing there is no marked accumulation (accumulation ratio of 1.4 – 1.5 for twice daily dosing), with steady state exposures achieved within 3 to 4 days.

Limited data suggest that the systemic exposure (AUC) of olaparib increases less than proportionally with dose over the dose range of 100 to 400 mg, but the PK data were variable across trials.

Co-administration with a high fat meal slowed the rate (T_{max} delayed by 2 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 20%).

Distribution

Olaparib had a mean (± standard deviation) apparent volume of distribution at steady state of 167 ± 196 L after a single 400 mg dose of olaparib. The *in vitro* protein binding of olaparib at plasma concentrations achieved following dosing at 400 mg twice daily is approximately 82%.

Metabolism

In vitro, CYP3A4 was shown to be the enzyme primarily responsible for the metabolism of olaparib. Following oral dosing of ^{14}C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%). It was extensively metabolized with unchanged drug accounting for 15% and 6% of radioactivity in urine and feces, respectively. The majority of the metabolism is attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulfate conjugation.

Excretion

A mean (± standard deviation) terminal plasma half-life of 11.9 ± 4.8 hours and apparent plasma clearance of 8.6 ± 7.1L/h were observed after a single 400 mg dose of olaparib.

Following a single dose of ^{14}C-olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via the urine and 42% via the feces. The majority of the material was excreted as metabolites.

Based on preliminary data from a dedicated renal impairment trial, the mean AUC and C_{max} of olaparib increased by 1.5and 1.2-fold, respectively, when olaparib was dosed in patients with mild renal impairment (CLcr = 50-80 mL/min; N=14) compared to those with normal renal function (CLcr >80 mL/min; N=8). There are no data in patients with CLcr < 50 mL/min or in patients on dialysis.

Drug Interactions

In vitro, olaparib was an inhibitor of CYP3A4 and an inducer of CYP2B6 at higher concentrations than are clinically achieved. Olaparib produced little/no inhibition of other CYP isozymes. *In vitro* studies have shown that olaparib is a substrate of CYP3A4.

Based on the data from a drug-interaction trial (N=57), the AUC and C_{max} of olaparib increased by 2.7- and 1.4-fold, respectively, when olaparib was administered in combination with itraconazole, a strong CYP3A inhibitor. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that a moderate CYP3A inhibitor (fluconazole) may increase the AUC and C_{max} of olaparib by 2- and 1.1-fold, respectively.

Based on the data from a drug-interaction trial (N=22), the AUC and C_{max} of olaparib decreased by 87% and 71%, respectively, when olaparib was administered in combination with rifampicin, a strong CYP3A inducer. Simulations using PBPK models suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC and C_{max} of olaparib by 50 - 60% and 20 - 30%, respectively. *In vitro* studies have shown that olaparib is a substrate of P-gp and an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is unknown.

For more information refer to the current version of the olaparib IB.

6.3 Androgen Deprivation Therapy (ADT)

Physician's choice of GnRH agonist/antagonist. A one month or three month formulation is acceptable. Casodex to prevent testosterone flare is allowed if a GnRH agonist is used.

6.4 Potential for drug-drug interactions

Medications with the potential for drug-drug interactions are listed in Appendix C.

6.5 Treatment Delay

Subjects receiving durvalumab or olaparib who require therapy delay of more than 8 weeks due to toxicity will be removed from treatment but will be followed according to the schedule of assessments. If toxicity is attributed to a single agent, upon discussion with the Sponsor Principal Investigator, subjects may continue the other drug.

7. SAFETY EVALUATION

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

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 related to the medicinal product.

An adverse event will be recorded and followed from informed consent to 30 days post treatment or resolution.

7.1.2 Expected Adverse Events

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

7.1.3 Unexpected Adverse Events

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product) (ICH E2A).

Contact the Sponsor Principal Investigator to confirm unexpected adverse events when necessary.

7.1.4 Serious Adverse Event (SAE)

An SAE as defined in the Code of Federal Regulations (21CFR312.32) is any event that:

- results in death
- is life-threatening
- results in inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity

- results in congenital anomaly or birth defect
- is medically significant in the opinion of the investigator

Hospitalizations that are **not** considered SAEs include:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

7.1.5 Progression of malignancy

Progression of a subject's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the subject's condition. If disease progression results in death or hospitalization while on study or within 30 days of the last dose, progressive disease will be considered an SAE.

7.1.6 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening "if, in the view of either investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death (FDA 21 CFR 312.32).

7.1.7 Hospitalization (or prolongation of hospitalization)

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent adverse event. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g., admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.8 Persistent or Significant disability/incapacity

Any AE that results in persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.

7.1.9 Congenital anomaly

If the female partner of a male patient becomes pregnant during the course of the study, the treating physician should be notified immediately. All confirmed pregnancies must be immediately reported to the PCCTC.

7.1.10 AEs of Special Interests (AESIs)

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 and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Sponsor Principal Investigator.

AESIs observed with durvalumab include:

- Rash / Dermatitis
- Diarrhea / Colitis
- Endocrinopathies (adrenal insufficiency, hyper- and hypothyroidism, hypophysitis/hypopituitarism, thyroiditis, and Type I diabetes mellitus)
- Hepatitis / transaminase increases
- Intestinal perforation
- Myocarditis
- Myositis / Polymyositis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Pneumonitis / ILD
- Other rare/less frequent events (including, but not limited to, haematological events, neuromuscular toxicities [such as Guillain-Barre syndrome and myasthenia gravis], non-infectious encephalitis, non-infectious meningitis, pericarditis, rheumatological events, sarcoidosis, skin events, uveitis [and other events involving the eye], and vasculitis). It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in Appendix G. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating

these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

AESIs observed with olaparib include:

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

Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE (e.g., non-melanoma skin cancer) or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

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 (see Appendix H) 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 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.

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.
- Saturation of peripheral oxygen (SpO2)

7.1.11 Hy's Law

Cases where a subject 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 Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

7.2 Recording and Grading of Adverse Events

7.2.1 Recording

All observed or volunteered adverse events, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be recorded.

A clinically significant change in a physical examination finding or an abnormal test result should be recorded as an AE, if it:

- is associated with accompanying symptoms
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study
- requires additional concomitant drug treatment or other therapy, or
- is considered clinically significant by the investigator or sponsor

An abnormal test result that is subsequently determined to be in error does not require recording as an adverse event, even if it originally met one or more of the above criteria.

7.2.2 Grading severity

All adverse events will be graded based on the NCI CTCAE version 5.0. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

7.2.3 Attributing causality

After assigning a grade to an adverse event, the investigator must evaluate all AEs for possible causal relationship to the investigational agent(s). Causality attribution will be decided using the criteria outlined in *Table **1***.

Table 1. Relationship of Adverse Event to Study Drug

Relationship	Description
Unrelated	AE is clearly not related
Unlikely	AE is doubtfully related
Possible	AE may be related
Probable	AE is likely related
Definite	AE is clearly related

7.3 Reporting Serious Adverse Events

7.3.1 Reporting serious adverse events

All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to the PCCTC within 24 hours of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:

- protocol # and title

- subject identification number, sex, age at event
- date the event occurred
- description of the SAE
- causal relationship to the study treatment(s)

The SAE Report Form will be used for reporting each SAE and should be submitted to the PCCTC Project Coordinator within 24 hours. The PCCTC will facilitate all SAE report form submissions to lead site/sponsor.

Grade, relationship, action taken, concomitant medications, outcome, etc. should be reported to the PCCTC as soon as possible.

Follow-up of adverse events should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator.

SAE contact information for the PCCTC is listed below.

PCCTC:
Prostate Cancer Clinical Trials Consortium
Email: pcctc@mskcc.org

The PCCTC will be responsible for reporting to AstraZeneca by facsimile any Serious Adverse Event that occurs during the SAE reporting period. The PCCTC will report the SAE within 24 hours of PCCTC first awareness of the event (immediately if the event is fatal or life-threatening).

The PCCTC will disseminate information regarding SAEs to the participating sites provided by AstraZeneca within five (5) days of review of the information by the Sponsor Principal Investigator (or her designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study medication.

The PCCTC will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

7.3.1 Serious Adverse Event Reporting to the FDA and AstraZeneca

It is the responsibility of MSKCC to submit an investigational new drug application (IND) or receive an IND exemption from the FDA for clinical trials conducted with investigational agents and to ensure that FDA and all participating investigators are promptly informed of significant new AEs or risks with respect to the investigational agent.

Serious, unexpected AEs believed to be definitely, probably, or possibly related to the study treatment will be reported to the FDA by MSKCC in accordance with IND regulations. AEs that must be reported to the FDA will also be concurrently submitted to AstraZeneca by the PCCTC. *A cover page should accompany the SAE form indicating the following:

- Investigator Sponsored Study (ISS)

- The investigator IND number assigned by the FDA, if applicable
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

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

* Send SAE report and accompanying cover page by way of email to AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE believed to be definitely, probably or possibly related to olaparib or durvalumab becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA if applicable.

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

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

An SAE which occurs after consent and before a subject starts study treatment does not need to be reported if it is unrelated to screening procedures. All SAEs that occur once a subject has started study treatment will be reported irrespective of causality. Non-serious AEs will be collected from the time consent is given, throughout the treatment period and up to and including the 30 days after the last dose of study drug, unless the toxicity is considered related to study drug. If related to study drug, non-serious AEs and SAEs will be collected from the time the consent is given, throughout the treatment period and up to and including the 90 days after the last dose of study drug. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for 90 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA, if applicable, and AstraZeneca). All study-related toxicities/SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

7.3.2 Reporting of paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab or olaparib therapy.

Pregnancy of the subject's partner is not considered to be an AE. However, if allow able per local procedures, 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 or olaparib if possible, will be followed up and documented.

7.3.3 Other events that require reporting

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

Any overdose of a study subject with durvalumab or olaparib, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to PCCTC. PCCTC will report to the sponsor and AstraZeneca/MedImmune Patient Safety or designee. If the overdose results in an AE, the AE must also be recorded as an AE (see Section 7.2). 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. There is currently no specific treatment in the event of an overdose of durvalumab or olaparib.

The investigator will use clinical judgment to treat any overdose.

New Cancer
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 IP and have been identified after the patient's inclusion in this study.

Hepatic function abnormality
Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study subject, 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 PCCTC, 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 is 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 subject will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject 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 (meeting criteria for Hy's Law as per above) will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

7.3.3 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of study drug must be reported to the PCCTC as follows:

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

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented, but will not be reported as an SAE.

The PCCTC will be responsible for reporting deaths to AstraZeneca.

7.4 Safety Reports

- PCCTC will distribute outside safety reports to the participating sites.
- Participating sites must submit safety reports to their institution's IRB/PBs per participating site guidelines.

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Therapeutic Response

8.1.1 PSA

This trial will measure PSA monthly for the first 24 months. The primary endpoint is an undetectable PSA at 24 months with non-castrate levels of testosterone (>150 ng/dL).

9. DATA REPORTING AND REGULATORY REQUIREMENTS

9.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

9.1.1 Electronic Case Report Forms (eCRFs)

Standardized eCRFs and CRF Completion Guidelines will be created by the PCCTC for the collection of study data. Access and training for PCCTC Medidata Rave EDC will be made available to participating sites upon local regulatory approval. The participating site investigator is responsible for ensuring eCRFs are completed accurately and in a timely manner.

9.1.2 Source documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation will be made available to support the subject's research record.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

9.2 Study Monitoring and Quality Assurance

9.2.1 Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSMP) at MSKCC were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials. The DSMPs at MSKCC were established and are monitored by the Office of Clinical Research.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. There are several committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the MSKCC Research Council and Institutional Review Board. As a moderate risk trial, this study will be monitored by DSMC twice per year.

9.2.2 Data Monitoring, Auditing, and Quality Assurance

In addition to review by DSMC, PCCTC will conduct regularly scheduled monitoring visits. Reports will be generated by the PCCTC to monitor subject accruals and the completeness of data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Sponsor Principal Investigator for discussion and action.

The monitoring visit will include a review of source documentation to evaluate:

- Regulatory/IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
- Protocol defined treatment compliance

- Subject records
  - A signed and dated informed consent form for each subject
  - Adherence to eligibility criteria
  - Source Data Verification for identified subjects

Monitoring findings will be reviewed and disseminated to the site investigators and staff.

The PCCTC may also perform site audits. If a site is notified of an external audit relating to this study, the site should notify the PCCTC immediately. The PCCTC and/or Monitors assigned to this study will provide site support during audits (quality control and/or regulatory agency) including review and assisting sites with responses to audit findings.

9.2.3 Data Review and Queries

The PCCTC will review data and source documentation. Data will be monitored and source data verified as defined in the Monitoring and Data Management plans and discrepancies will be issued as queries in the EDC. In addition, the PCCTC will review data for logic, consistency, and obvious anomalies.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Primary endpoint

Undetectable PSA with recovered testosterone (non-castrate defined as testosterone > 150ng/dL) at 24 months. Undetectable is defined as PSA < 0.05 ng/ml. For institutions where the lower limit of detectable is 0.10 ng/ml, then undetectable will be defined as PSA <0.10 ng/ml.

10.1.3 Secondary endpoints

- Undetectable PSA at 5 months (with the combination of durvalumab and olaparib, no ADT)
- Safety of the combination of durvalumab and olaparib will be determined by the summary of AEs

10.1.4 Exploratory endpoints/correlative studies

- Measurement of patient reported toxicities using PRO-CTCAE at screening, cycle 5, cycle 11, and EOT. Changes over time and comparison to clinician reported toxicities (CTCAE v5.0)
- Blood biomarkers at cycle 1, cycle 2, cycle 5, cycle 11, and end of treatment: PBMCs collected to assess immunomodulation, for example, changes in T -cell populations over time, multiplex cytokine analysis, tumor associated antigens; cfDNA will also be collected at cycle 1, cycle 5 and end of treatment for potential future use.
- Archival tissue for analysis of immune activating genes and PDL1 expression
- Undetectable PSA at 11 months (irrespective of testosterone level)
- PSA PFS
- Change in PSA doubling time relative to trial entry

10.2 Sample Size Determination

The primary objective of the study is to determine the efficacy of the combination of olaparib with durvalumab in subjects with biochemically recurrent castration sensitive disease. The primary endpoint of the study is maintaining an undetectable PSA with recovered testosterone at 24 months and this event is defined as a success. Subjects that withdraw prior to the 24 month follow up time are deemed as failures for the primary endpoint. A single stage design that differentiates between population success rates of 0.15 and 0.35 will be used to assess treatment activity.[63]

Thirty-two subjects will be accrued to this trial. If eight or more successes are observed, it is concluded that the therapy is sufficiently active to warrant further study. This design has power greater than 0.90 for a population success proportion of 0.35 using a one-sided test with size 0.10 for the population success rate 0.15.

In addition to the evaluation of the primary endpoint, the study will be monitored for unacceptable toxicity, which is defined as Grade 3 or greater immune related toxicity requiring steroids or ≥ Grade 3 non-immune toxicity requiring trial discontinuation. The stopping rule for excessive toxicity and the corresponding power calculation is provided in the table below.

Toxicity	# of toxicities needed to stop the study	Toxicity rate in the population	Probability boundary is crossed
≥ Grade 3 immune related toxicity requiring steroids or ≥ Grade 3 non-immune toxicity requiring trial discontinuation	4 in the first 8 subjects 5 in the first 16 subjects 7 in the first 24 subjects 9 within 32 subjects	0.15	0.11
		0.35	0.89

10.3 Analysis Populations

10.3.1 Intent-to-treat/Response-to-treatment/Evaluable population

All subjects who meet eligibility criteria and receive at least one dose of study drugs will be included in the main analysis of efficacy, even if there are major protocol deviations (e.g., incorrect treatment schedule or drug administration).

Conclusions are to be based on the population of all eligible subjects. Subanalyses may be performed on various subsets of subjects, such as those with no major protocol deviations or those who continued in the study for the entire treatment period (i.e., did not withdraw prematurely). Subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy.

10.3.2 Safety population

All subjects enrolled in the study who receive at least one dose of study drugs will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose.

10.4 Safety Analysis

10.4.1 Evaluation of adverse events

Treatment-emergent adverse events will be summarized (number and percentage of subjects) for all subjects who receive at least one dose of both investigational therapies. Adverse event summaries will be organized by body system, frequency of occurrence, intensity (i.e., severity grade), and causality or attribution. Subjects who experience an adverse event more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

10.4.2 Evaluation of serious adverse events and premature withdrawals

Adverse events deemed serious and those resulting in treatment withdrawal or death will be summarized separately.

10.4.3 Evaluation of laboratory parameters and assays

Selected clinical laboratory parameters will be summarized and clinically significant changes from baseline will be discussed.

10.4.4 Extent of exposure

Treatment exposure will be summarized for all subjects, including dose administration, number of cycles, dose modifications or delays, and duration of therapy.

10.5 Statistical Procedures and Analysis

Summary statistics include the number of observations, mean, standard deviation, median, minimum, and maximum values.

Statistical methods for the analyses

An exact binomial test will be used to evaluate the efficacy of the 24 months undetectable PSA endpoint. In addition, the proportion of subjects that attain an undetectable PSA at (1) 5 months, (2) 11 months, and (3) 24 months will be computed along with their attendant 95% confidence intervals. The probability of PSA progression over time will be estimated using the cumulative incidence function.

A paired t-test will be used to compare the PSA doubling time at 24 months to the PSA doubling time at study entry.

Kendall's tau with longitudinal data will be used to compare patient recorded toxicities to physician recorded toxicities over time.

The immunologic profile of patients over time will be described using nonparametric kernel smoothing.

11. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, as adopted by applicable laws and regulations, and the ethical standards set forth in the Declaration of Helsinki (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

11.2 Protocol Amendments

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics Committee (IEC). Amendments to the protocol may be made only with consent of the lead site/sponsor and PCCTC and are subject to IRB approval before instituting.

11.3 Written Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the subject. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an adverse event occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the subject.

Subjects will be required to sign and date an informed consent form that meets the requirements of the Code of Federal Regulations and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the subject is enrolled in the study.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol
- the right of the subject to accept or refuse treatment and to withdraw from participation in this study
- Text regarding the consortium and the coordinating center should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (e.g., "Prostate Cancer Clinical Trial Consortium")

11.4 Protection of Privacy

Subjects will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the subject's medical records, and each subject will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the investigator and approved by the IRB.

11.5 Terminating or Modifying the Study

Adverse event and laboratory data from this trial will be assessed by the Sponsor Principal Investigator on an ongoing basis. SAEs will be reviewed as they are reported to the sponsor and PCCTC, and the Sponsor Principal Investigator will make an assessment regarding the safety of

continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the principal investigator be that the study should be terminated, the study will be closed to further accrual. Subjects who are receiving an investigational agent(s) will be assessed individually by the investigator to see if it is in the subjects' best interest to continue, which might be the case for a subject that is responding to the intervention. Follow-up safety assessments will be performed for all subjects who are terminated from the study prematurely.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**%**	**Description**
0	Normal activity. Fully active, able to continue all predisease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair > 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX B: STUDY CALENDAR

(A cycle = 28 days; a month = 28 days)

	Screening		Treatment/Intervention Period									End of Treatment (EOT) within 30 days of last dose	Follow Up [s]
			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7- Cycle 24		
	Day -42 to Day -1	Day -14 to Day -1	Day 1 (±3 d)	Day 15, (±3 d)	Day 1 (±3 d)	Day 15 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)		(±7 d)
Informed consent and research authorization/ HIPAA form [a]	X												
Demographics, medical history, histologic confirmation	X												
Physical examination, Vitals (Blood Pressure, Pulse Temperature), weight [b]	X		X	X	X	X	X	X	X	X	X	X	X
Height	X												
12-lead EKG	X												

	Screening		Treatment/Intervention Period									End of Treatment (EOT) within 30 days of last dose	Follow Up [s]
			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7-Cycle 24		
	Day -42 to Day -1	Day -14 to Day -1	Day 1 (±3 d)	Day 15, (±3 d)	Day 1 (±3 d)	Day 15 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)		(±7 d)
Performance status	X		X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	
Adverse Events	X		X	X	X	X	X	X	X	X	X	X	
Radiologic evaluations and measurements [c]	X		For non-metastatic, rising PSA subjects, radiologic tests are performed at Cycle 5 (+/- 2 week), Cycle 24 (+/- 2 week) or at EOT (+/- 2 week) if discontinued sooner.									X [d]	
CBC w/ diff plts [e]		X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel [f]		X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests [g]		X											
PSA [h]		X	X		X		X	X	X	X	X	X	X
TFTs [i]		X			X			X		X	X		X
Testosterone [j]		X								X	X		
Hepatitis Panel		X											
HIV		X											
Urinalysis [k]		X											

	Screening		Treatment/Intervention Period									End of Treatment (EOT) within 30 days of last dose	Follow Up [s]
			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7-Cycle 24		
	Day -42 to Day -1	Day -14 to Day -1	Day 1 (±3 d)	Day 15, (±3 d)	Day 1 (±3 d)	Day 15 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)	Day 1 (±3 d)		(±7 d)
PBMC [l]			X		X				X		X	X	
PRO-CTCAE [m]	X								X		X	X	
cfDNA [n]			X						X			X	
PDL-1 Expression (archived tissue) [o]	X												
Tissue Sequencing [p]	X												
Normal Sample [q]	X												
Olaparib Administration [r]			X										
Durvalumab Administration [r]			X										
ADT Administration [r]			X										

a. Informed consent and radiologic assessments should be obtained within 42 days.
b. Refer to section 6.1 for monitoring of vital signs and observation period.

c. Radiographic evaluations will include CT CAP with contrast or MRI with contrast of the abdomen and pelvis, and CT chest without contrast. Radionuclide bone scan will be performed. All disease sites must be assessed using the same methodology as performed at baseline. At the discretion of the investigator, additional radiological evaluations may be performed at an unscheduled time point.
d. If radiographic evaluations were completed within 30 days of EOT, they do not need to be repeated.
e. CBC w/diff, platelets will be monitored biweekly during Cycle 1 and 2, and monthly from Cycle 3-Cycle 24 (see section 5.1.9 for additional information regarding laboratory tests)
f. CMP will be monitored biweekly during Cycle 1 and 2, and monthly from Cycle 3-Cycle 24 (see section 5.1.9 for additional information regarding laboratory tests)
g. APTT and INR. See section 5.1.9 for more information on coagulation tests.
h. PSA will be collected monthly during each cycle.
i. Thyroid function tests (TFTs), including TSH, free T4, and free T3 will be monitored every other cycle (beginning with Cycle 2, Cycle 4, Cycle 6, etc.)
j. Testosterone will be monitored at Screening, Cycle 6, Cycle 11 and every other month from Cycle 12-Cycle 24
k. Urinalysis: to be collected at screening. If clinically indicated, urinalysis should be performed while on treatment. See section 5.1.9 for additional information.
l. Peripheral Blood Mononuclear Cells (PBMCs) will be drawn C1D1 before treatment, Cycle 2, Cycle 5, Cycle 11, and EOT.
m. QoL Assessment (PRO-CTCAE) compared from screening, Cycle 5, Cycle 11, and EOT.
n. Non-immune blood biomarkers: cfDNA from C1D1 before treatment, Cycle 5, and EOT.
o. Tissue biomarkers: PDL1 expression at screening.
p. Tissue sequencing does not need to be repeated if performed prior to consent and subject has a confirmed DDR mutation. If DDR mutation status is unknown or sequencing was not previously performed, archival tissue as well as a matched normal sample must be sent for Next Generation Sequencing. If available, additional archival tissue from all subjects should be sent and banked for future analysis of immune markers.
q. A blood or saliva sample will be collected during screening as matched normal for sequencing for patients completing prospective Next Generation Sequencing using assays that require a matched normal sample.
r. Subjects will be treated concurrently with olaparib + durvalumab continuously for 24 months. Durvalumab will be administered on Day 1 of each cycle (±3). After the first 4 months, if a subject fails to achieve an undetectable PSA [PSA of <0.05 (or PSA <0.10 for institutions where this is the lower limit of detection] with the combination of olaparib and durvalumab, ADT will be added for 6 months (starting at Cycle 5) while continuing treatment with olaparib and durvalumab (see section 6.3 for additional details regarding ADT). For subjects who have an undetectable PSA after the first 4 months of treatment, they will continue on the combination of olaparib + durvalumab continuously for 24 months (without ADT). As long as it is believed that subjects are clinically benefiting, they will remain on treatment for up to 24 months with olaparib and durvalumab. For example, a subject with a PSA reduction that does not achieve an undetectable PSA would be allowed to remain on study for the duration of the trial. Subjects who meet progression criteria while on active therapy would come off of trial.
s. Subjects who have an undetectable PSA after completion of protocol therapy will be followed every 12 weeks. PSA, CMP, CBC, and TFTs should be performed. A physical exam will be performed. Subjects who respond and later progress in the first year following the 24 month treatment phase will be allowed to re-induce with the combination and will restart their calendar with C1D1 if they continue to meet all clinical eligibility criteria are met. PCCTC must review the confirmation of eligibility prior to re-inducing treatment.

APPENDIX C. ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

Introduction

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

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

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

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

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 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).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

Identification of Potential Hy's Law Cases

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

- ALT ≥ 3xULN
- AST ≥ 3xULN

- TBL ≥ 2xULN

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

- Notify the PCCTC. The PCCTC will notify AstraZeneca when appropriate.
- Determine whether the subject meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

Potential Hy's Law Criteria met

- Notify the PCCTC. The PCCTC will notify AstraZeneca when appropriate.

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

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Sponsor Principal Investigator.
- Enter data into the CRFs as information becomes available
- If at any time (in consultation with the Sponsor Principal Investigator) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Sponsor Principal Investigator contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Lead Principal Investigator, PCCTC and AstraZeneca may also be involved in this review together with other subject matter experts as appropriate.

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

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

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

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

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

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation': http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX D: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure subject safety, the following potent inhibitors of CYP3A4 must not be used during this study for any subject receiving olaparib.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions.

Prohibited Concomitant Medications while subjects are taking Olaparib:

Agent	Agent
ketoconazole	rifapentine
itraconazole	rifabutin
ritonavir	carbamazepine
indinavir	phenobarbitone
saquinavir	nevirapine
telithromycin	modafinil
clarithromycin	St John's Wort (*Hypericum perforatum*)
nelfinavir	
phenytoin	
rifampicin	

After enrollment if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the subject's safety and welfare, the Sponsor Principal Investigator must contact the AstraZeneca Study Physician. A decision to allow the subject to continue in the study will be made on a case-by-case basis.

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 100mg BID 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 150mg BID 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 or Moderate CYP3A inducers

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

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

If a subject requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of olaparib.

P-gp inhibitors

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

Effect of olaparib on other drugs

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

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

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

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

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

Natural/Herbal Products

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF).

It is not recommended to consume grapefruit juice while on olaparib therapy.

Vaccines

Live virus and live bacterial vaccines, with the exception of shingles vaccine (live), should not be administered while the subject is receiving study medication until 30 days after the last dose of study therapy.

Anticoagulant Therapy

Subjects 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.

Anti-emetics/Anti-diarrheal

If a subject develops nausea, vomiting and / or diarrhea, then these symptoms should be reported as AEs and appropriate treatment of the event given.

Administration of other anti-cancer agents

Subjects must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted while the subject is receiving study medication.

APPENDIX E: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	androgen receptor
ASAEL	Agent Specific Adverse Event List
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
CAEPR	Comprehensive Adverse Event and Potential Risks
CBC	complete blood count
CDE	common data element
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	trough observed concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
DLT	dose-limiting toxicity
DSMB	data and safety monitoring board
DSMC	data and safety monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG-PET	2-[18F]fluoro-2-deoxyglucose positron emitting tomography

FDHT	18-fluoro-dehydrotestosterone
FISH	fluorescence in situ hybridization
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
HDAC	histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HRPC	hormone-refractory prostate cancer
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunochemical
IIT	investigator-initiated trial
imAE	immune-mediated adverse event
IND	investigational new drug
IO	Immuno-oncology
IRB	Institutional Review Board
ITT	intent-to-treat population
IV	intravenous
LD	longest diameter
LDH	lactate dehydrogenase
LOI	letter of intent
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
N	number of subjects or observations
N/A	not available
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NOS	not otherwise specified
NSAID	nonsteroidal anti-inflammatory drug
PBMCs	peripheral blood mononuclear cells
PCCTC	Prostate Cancer Clinical Trials Consortium
PCRP	Department of Defense Prostate Cancer Research Program
PCWG2, PCWG3	Prostate Cancer Working Group

PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PMB	Pharmaceutical Management Branch
PO	per os (by mouth)
PR	partial response
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSMA	prostate specific membrane antigen
QC	quality control
qd	quaque die (every day)
qRT-PCR	quantitative reverse transcription-polymerase chain reaction
QOL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
RPC	eResearch Program Coordinator
RSA	Research Study Assistant
SAE	serious adverse event
SD	standard deviation
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedures
SPORE	Specialized Programs of Research Excellence
SUV	standardized uptake value
$t_{1/2}$	terminal half-life
TDP	time to disease progression
T_{max}	time of maximum observed concentration
TMPRSS2	transmembrane protease, serine 2
TNM	tissue, lymph node, metastases
ULN	upper limit of normal
Vss	volume of distribution at steady-state
WBC	white blood cell
WHO	World Health Organization

APPENDIX F. SELECT PRO - CTCAE

APPENDIX G. DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR DURVALUMAB

The below table represents recommended management of imAE. These represent guidelines, not mandates of the study protocol.

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., NCCN, 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 immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. 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 should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) 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 need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and 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.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; ESMO European Society for Medical Oncology

Specific Immune-Mediated Reactions

Adverse Event	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 CTC grade/severity)	General Guidance	**For Any Grade:** – Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated 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 aetiologies 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, and high- resolution CT scan. – Consider Pulmonary and Infectious Disease 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 worsens, then treat as Grade 3 or Grade 4. 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.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider Chest CT with contrast and repeat in 3-4 weeks – 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 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). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.

			– Consider, as necessary, discussing with Sponsor Principal Investigator.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	– **For Grade 3 or 4** Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults, consider discussing with Sponsor Principal Investigator as needed. – Hospitalize the subject. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 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). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade**	General Guidance	**For Any Grade:** – 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). – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – 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. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, to prevent potential progression to higher grade event including intestinal 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 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 worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a GI specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressives 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.[a] **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with Sponsor Principal Investigator if no resolution to Grade ≤1 in 3 to 4 days.
Grade 3 or 4	**Grade 3** For patients treated with PD-1 or PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. Permanently discontinue study drug	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 days continue steroids and promptly add further immunosuppressives agents (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) – **Caution:** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade large intestine perforation/Intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis (elevated LFTs) 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 CTC grade/severity)	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1	No dose modifications. If it worsens, then treat as Grade 2.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve. – If no resolution to Grade ≤1 in 1 to 2 days, consider discussing with the Sponsor Principal Investigator 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.
	Grade 3 or 4	**For Grade 3:**	**For Grade 3 or 4:**

		For elevations in transaminases ≤8 × ULN, or elevations in total bilirubin ≤5 × ULN: Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. **For Grade 4:** 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 immunosuppressant therapy (mycophenolate mofetil 0.5- 1g every 12 hours then taper in consultation with hepatology consult). Discuss with Sponsor Principal Investigator if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Consult a nephrologist. – 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). – Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider using steroids in the absence of clear alternative etiology even for low-grade events (Grade 2), to prevent potential progression to higher grade event.
Grade 1	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to >1 to 1.5 x baseline, consider following recommendations in this row.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If toxicity worsens, then treat as Grade 3 or 4. If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond >3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 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. – 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 or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup and prompt treatment with an immunosuppressive in consultation with a nephrologist.
Rash or Dermatitis (Including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – Hold study drug if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or other severe cutaneous adverse reaction (SCAR) is suspected. – **Permanently** discontinue study drugs if SJS, TEN or SCAR 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., e.g., emolient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. If toxicity worsens, then treat as Grade 3. If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – 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 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Sponsor Principal Investigator and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If toxicity improves to Grade ≤1 or baseline, then resume	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines].

		drug/study regimen after completion of steroid taper. If toxicity worsens, then treat as Grade 4. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consider skin biopsy (preferably more than 1) as clinically feasible. – Consider, as necessary, discussing with Sponsor Principal Investigator.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated if 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
	For Grade 1:	No dose modifications	
	For grade 2, 3, or 4:	**For Grade 2, 3, or 4** In consultation with relevant pancreatic 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 CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider gastroenterology referral
	Grade 1	**For Grade 1:** No dose modifications	**For Grade 1:** – IV hydration – Manage per amylase/lipase increased (asymptomatic)
	Grade 2, 3, or 4	**For Grade 2:** Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2, 3, or 4:** - Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent - IV hydration

		For Grade 3 or 4: Permanently discontinue study drug/study regimen	
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Sponsor Principal Investigator. – Monitor subjects 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. – Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – 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. – If a subject 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.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor subject with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning 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). – 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 other than hypothyroidism and type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve. Study drug/study regimen can be resumed once subject stabilizes and after completion of steroid taper. Subjects 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 investigator or treating physician's clinical judgement. If toxicity worsens, then treat based on severity.	**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 subjects with abnormal endocrine work up, except for those with isolated hypothyroidism or type 1 DM, 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 (e.g., hydrocortisone, or sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 diabetes mellitus (DM) 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. – For subjects with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**For Any Grade:**	**For Any Grade:** – Subjects should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**

	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2:** – Consider, as necessary, discussing with the Sponsor Principal Investigator. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG or other immunosuppressive depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with the Sponsor Principal Investigator. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressants (e.g., IV IG or other immunosuppressant depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special

	defining the CTC grade/severity)		care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Subjects should be evaluated to rule out any alternative etiology (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 subjects 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, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Consider discussing with the Sponsor Principal Investigator. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. – Consult a Neurologist.
	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 or autonomic instability.	**For Grade 2:** – Consider discussing with the Sponsor Principal Investigator. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). MYASTHENIA GRAVIS: o Steroids may be successfully used to treat myasthenia gravis. It is important to consider

		that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each subject. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis GUILLAIN-BARRE: o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**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 or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider discussing with the Sponsor Principal Investigator. Recommend hospitalization. – Recommend hospitalization – Monitor symptoms and obtain neurological consult. MYASTHENIA GRAVIS: o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis GUILLAIN-BARRE: o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

			○ Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in subjects with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Sponsor Principal Investigator. – Monitor subjects 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). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, 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. – Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. – Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4	**Grade 2:** Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and

		decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. **Grade 3:** Permanently discontinue study drug/study regimen.	when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). 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	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Monitor subjects for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; 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 Sponsor Principal Investigator. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein 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).

	Grade 1	No dose modifications.
	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.
	Grade 3 or 4	**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 4:** Permanently discontinue study drug/study regimen.	– 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). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether subject may require IV IG, plasmapheresis.

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

[c]NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC 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).	– The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – 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 other society guidelines (e.g., NCCN, ESMO)
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 Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor subjects 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 standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC 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	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

APPENDIX H. DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR OLAPARIB

Olaparib dose reductions based on hematologic nadir

Granulocytes and Platelets	Olaparib Dose Adjustment
ANC < LLN* but ≥1000/mm3 and/or PLT<LLN but ≥50,000/mm3 (CTCAE Grade 1-2)	Investigator judgment to continue study treatment in full dose or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
ANC<1000/mm3 and/or PLT<50,000/mm3 (CTCAE Grade 3 - 4)	Hold olaparib. Once toxicity resolves to Grade 1, olaparib may be continued -1 dose level.

*LLN = lower limit of normal

- If the ANC nadir is under 1000/mm3 (CTCAE Grade 3 - 4) and/or the platelet nadir is under 50,000/mm3 (CTCAE Grade 3 - 4) after a 1 dose level reduction of olaparib, then the next cycle will be started at -2 dose level once toxicity resolved to CTCAE Grade 1 or better
- Subjects requiring more than two dose reductions will discontinue olaparib

Management of toxicity related to olaparib

Any toxicity observed during the course of the study could be managed by interruption and/ or dose reduction of the dose if deemed appropriate by the Investigator. Olaparib must be interrupted until the subject recovers completely or the toxicity reverts to the NCI-CTCAE Grade 1 or less. If olaparib is delayed more than 8 weeks for any reason, or if a dose reduction below 200 mg daily is required, subjects will discontinue treatment with olaparib.

- Where toxicity reoccurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the subject should be considered for dose reduction or must permanently discontinue treatment with olaparib.
- Treatment must be interrupted if any NCI-CTCAE Grade 3 or Grade 4 AE occurs which the Investigator considers to be related to administration of olaparib.

Adverse Event with Possible Relationship to Olaparib		**Action to Take**
Non-hematologic toxicities including nausea, vomiting, and diarrhea	Grade 1 and Grade 2	If subjects develop intolerable Grade 1 or Grade 2 toxicities (per subject) then they can undergo a dose reduction. For Grade 4 toxicities despite optimal medical therapy, hold olaparib until equal or under Grade 1. Resume at one dose level reduction. Events of nausea and vomiting are known to be associated with olaparib treatment. In study, they are generally mild to moderate (CTCAE Grade 1 or Grade 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

		No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, subjects 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
General non-hematologic toxicities excluding nausea, vomiting, and diarrhea	Grade 3 or higher toxicities	Delay until recovery to Grade 1 or lower and reduce one dose level to 250mg BID). A maximum of 2 dose reductions can be made for repeat toxicity.
Anemia	CTCAE Grade 1 or Grade 2 (Hemoglobin (Hb) > 8 g/dl)	Investigate and manage as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anemia. Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases, management of anemia may require blood transfusions.
	CTCAE Grade 3 (Hb < 8g/dl) or worse	Study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the subject should be managed appropriately. Study treatment can be restarted at the reduced dose if Hb has recovered to > 10 g/dl. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require a further study treatment dose reduction to 200 mg BID. If a subject has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be permanently discontinued.
Neutropenia and leukopenia	CTC Grade 3 or worse neutropenia occurs	Manage as deemed appropriate by the investigator with close follow up and interruption of study drug. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a subject 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 of the last dose of study treatment. Study treatment can be restarted at the same dose if an AE of neutropenia or leukopenia have been recovered up to CTC AE Grade less than or equal to Grade 1 (ANC > 1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF). Any subsequent interruptions will require study treatment dose reductions to 250 mg BID as a first step and to 200 mg

		BID as a second step for a 300 mg monotherapy starting dose
Thrombocytopenia	CTCAE Grade 3 or worse	Study treatment should be interrupted for a maximum of 4 weeks. In some cases, management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines. Any subsequent interruptions will require study treatment dose reductions to 250 mg BID as a first step and to 200 mg BID as a second step for a 300 mg monotherapy starting dose
Prolonged hematological toxicities while on study treatment	≥2 week interruption/delay in study treatment due to CTC Grade 3 or worse anemia and/or development of blood transfusion dependence ≥2 week interruption/delay in study treatment due to CTC Grade 3 or worse neutropenia (ANC < 1 x 10^9/L) ≥2 week interruption/delay in study treatment due to CTC Grade 3 or worse thrombocytopenia (Platelets < 50 x 10^9/L)	Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x hematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) (1, 2) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the subject 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 haematological practice.
		Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for subjects with prolonged hematological toxicities. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued, and a full description of findings should be submitted with an SAE report (see Section 7.3 – Reporting of SAEs for reference) to the PCCTC. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.
Pneumonitis	Suspected or any grade	If subjects present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs in the absence of a clear diagnosis, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the subject treated appropriately.
Renal Impairment	Creatinine clearance below threshold for study inclusion (51ml/min)	If subsequent to study entry and while still on study therapy, a subject's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly. A dose reduction is recommended for subjects who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and

		50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg BID. Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted. Olaparib has not been studied in subjects with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if subjects develop severe impairment or end stage disease is it recommended that olaparib be discontinued.