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Immunotherapy in Patients with Metastatic Cancers and CDK12 Mutations

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IMPACT: Immunotherapy in Patients with Metastatic Cancers and CDK12 Mutations

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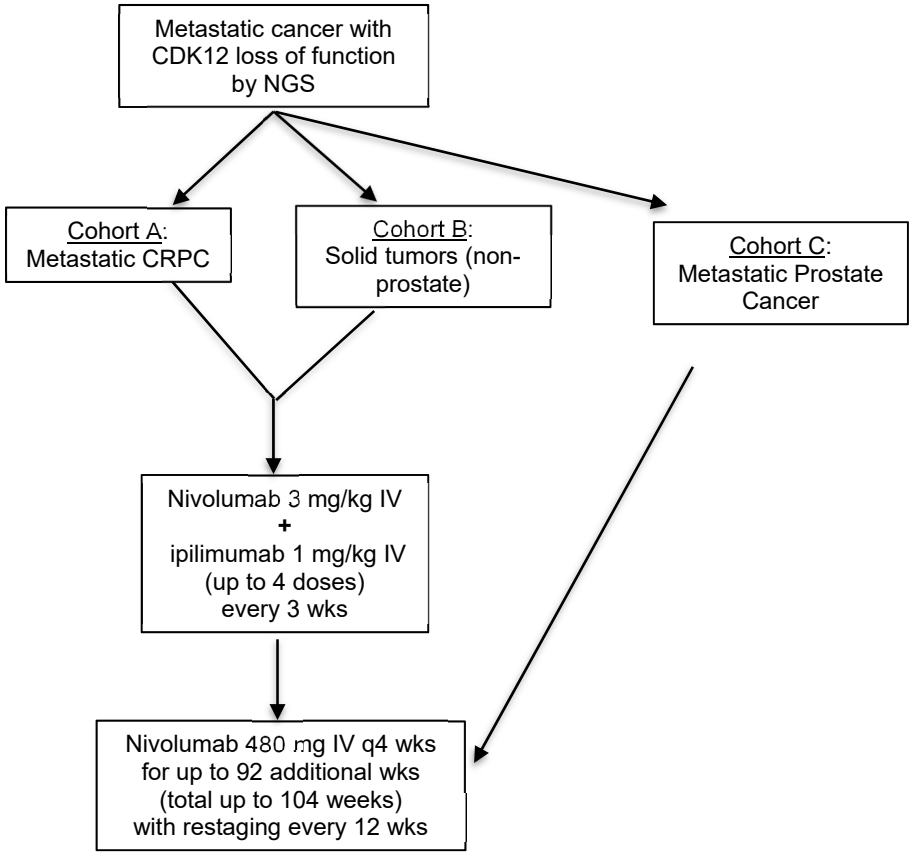
ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDK	Cyclin-Dependent Kinase
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte Antigen-4
CTSU	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HR	Homologous Recombination
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
mCRPC	Metastatic Castrate Resistant Prostate Cancer
MMR	Mismatch Repair
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PARP	Poly (ADP-ribose) Polymerase
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PDL1	Programmed Death Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PO	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
RPFS	Radiographic Progression Free Survival
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase

SPGT	Serum Glutamic Pyruvic Transaminase
UaP	Unanticipated Problem
WBC	White Blood Cells
WXS	Whole Genome Sequencing

STUDY SCHEMA

This is a multi-center, open label, 3 cohort study of patients with metastatic cancer, either metastatic castration resistant prostate cancer, or metastatic non-prostate cancer whose tumor harbors CDK12 loss of function. Patients with metastatic castration resistant prostate cancer (mCRPC) will be enrolled in cohort A or C, and patients with all other metastatic subtypes will be enrolled in cohort B. Cohorts A and B patients will begin receiving combination therapy with nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV every 3 weeks for up to 4 cycles if tolerated, followed by nivolumab maintenance therapy at flat dose 480 mg IV every 4 weeks through the end of the planned study duration, for up to 104 weeks of total therapy. Cohort C patients will receive nivolumab at flat dose 480 mg IV every 4 weeks for up to 104 weeks of total therapy. Cohort C will open after enrollment is complete to Cohort A.



STUDY SYNOPSIS

Title	IMPACT: Immunotherapy in Patients with Metastatic Cancers and CDK12 Mutations
Phase	Phase II
Methodology	Open label, 3 non-randomized cohorts
Study Duration	72 months
Study Center(s)	Multi-site; this is a multicenter trial including the lead site University of Michigan
Objectives and Endpoints	Primary Objective: To determine the efficacy of checkpoint inhibitor immunotherapy, nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only, in patients with metastatic prostate cancer harboring loss of CDK12 function. Secondary Objectives: 1. To determine the efficacy of checkpoint inhibitor immunotherapy,nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only, in patients with metastatic non-prostate cancer harboring loss of CDK12 function. 2. To determine the safety and tolerability of, nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only, in patients with metastatic cancers with loss of CDK12 function. 3. To evaluate other measures of clinical efficacy of checkpoint inhibitor immunotherapy in metastatic tumors with loss of CDK12 function. 4. To assess the Quality of Life (QoL) in subjects treated on protocol therapy. Exploratory Objectives: 1. To assess changes in the tumor genome with therapy. 2. To profile immune infiltration in tumor biopsies. **Endpoints** Primary Endpoint: The overall response rate (ORR) in subjects with metastatic castration resistant prostate cancer whose tumors harbor a genomic change resulting in CDK12 loss of function and who are treated with, nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only, as measured by PSA 50% decline from baseline as determined by PCWG3 criteria. Secondary Endpoints: 1. The overall response rate (ORR) in patients with metastatic non-prostate cancer harboring loss of CDK12 function, who are treated with nivolumab and ipilimumab combination

	therapy followed by nivolumab monotherapy, as measured by RECIST 1.1 criteria. 2. The frequency and severity of adverse events, as assessed by CTCAE version 4.03 criteria, in patients with metastatic cancer harboring loss of CDK12 function treated with, nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only. 3. Assess the radiographic progression-free survival (rPFS), progression-free survival (PFS), duration of response (DOR) among responders, duration of therapy (DOT), time to progression (TTP), overall survival (OS) and objective tumor response in patients with measurable disease by RECIST 1.1 criteria. For subjects with metastatic CRPC, determine the PSA progression-free survival and time to PSA progression by PCWG3 criteria. 4. Measure the Quality of Life (QoL) in subjects treated on protocol therapy using EORTC-QLQ-C30 and BPI-SF. <u>Exploratory Endpoints</u> 1. Tumor genome profiling by integrated DNA and RNA sequencing (including molecular tumor burden assessment) at baseline and optionally at progression. 2. Profiling of Immune infiltration in tumor biopsies.
Number of Subjects	25 mCRPC each in Cohorts A and C; and15 of non-prostate in Cohort B, 65 total subjects
Key Inclusion Criteria	1. Age ≥ 18 years and ability to understand and the willingness to sign a written informed consent. 2. ECOG performance status of 0, 1 or 2. 3. Subjects must have histologic or cytologic or radiographic evidence of metastatic adenocarcinoma of the prostate without small cell histology OR another type of metastatic carcinoma. Radiologic or pathologic evidence of metastases is allowed. 4. All subjects, regardless of cancer type, must have documented CDK12 loss on a CLIA approved, CAP certified next generation sequencing assay (tissue, cell-free DNA or other is allowed). (Further details section 3.1.4.) 5. Subjects with prostate cancer must have documented prostate cancer progression within six months prior to screening with PSA progression defined as a minimum of two rising PSA levels at least ≥ 1; one week between each assessment with at least one of those baseline PSA values ≥ 2 ng/mL, including after first generation anti-androgen withdrawal.

	6. Subjects with prostate cancer must have ongoing androgen deprivation with total serum testosterone < 50 ng/dL (or < 0.50 ng/mL or 1.73 nmol/L). If the subject is currently being treated with LHRH agonists (subjects who have not undergone an orchiectomy), this therapy must have been initiated at least 4 weeks prior to first dose of trial treatment. This treatment must be continued throughout the study. 7. Subjects with non-prostate histologies must have RECIST 1.1-measurable cancer on computed tomography (CT) or magnetic resonance imaging (MRI) scans. 8. Subjects must have recovered to baseline or ≤ grade 1 CTCAE v 4.03 from toxicities related to any prior treatments unless AE(s) are clinically non-significant and/or stable. 9. Patients must be ≥ 2 weeks from most recent systemic therapy or most recent radiation therapy. 10. Women of childbearing potential must have a negative serum or urine pregnancy test within 28 days prior to registration. Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, are naturally postmenopausal for at least 12 consecutive months or have undergone surgical removal of the ovaries. 11. Female and male subjects of reproductive potential must agree to use an adequate method of contraception starting with the first dose of study therapy through 5 months (for women) and 7 months (for men) after the last dose of study therapy. 12. Adequate organ function with absolute neutrophil count (ANC) ≥ 1,000/mm^3, hemoglobin ≥ 8.0 g/dL with or without pRBC transfusion; bilirubin/ALT/AST ≤ 2.5 x upper limit of normal (patients with known Gilbert disease who have serum bilirubin ≤3x ULN may be enrolled); serum creatinine <3.0 mg/dL or if elevated, a calculated estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2.
Key Exclusion Criteria	1. Prior treatment with anti-PD-1/PD-L1 and anti-CTLA-4 is NOT allowed. 2. Treatment with any investigational agent within 28 days prior to registration on this protocol. 3. Prior or concurrent malignancy that has needed active interventional systemic therapy in the last 2 years. Adequately treated basal cell or squamous cell skin cancer, non muscle-invasive urothelial cancer, or in situ cervical cancer are permitted. For subjects in the non-prostate cancer cohort, localized or locally advanced prostate cancer definitively treated without recurrence or with biochemical recurrence only are permitted.

	4. History or risk of any significant autoimmune diseases are excluded, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bells' palsy, Guillain-Barre syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. Vitiligo, mild psoriasis (topical therapy only) or hypothyroidism are allowed. No prior history of autoimmune pneumonitis allowed. Patients with previous drug-related or radiation therapy-associated pneumonitis that has since resolved are allowed. 5. Need for systemic corticosteroids > 10 mg prednisone daily or equivalent alternative steroid or other systemic immunosuppressive agents (such as cyclosporine or methotrexate). Physiologic doses of steroid for adrenal replacement therapy; topical and inhaled corticosteroids are permitted. 6. Any history of organ allografts. 7. Must not have known active hepatitis B, hepatitis C, or HIV seropositivity. Negative PCR suggests infection is not active or latent; however testing is not required in the absence of clinical suspicion.
Study Product(s), Dose, Route, Regimen	• Nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV every 3 weeks for up to 4 doses (12 weeks)-Cohort A and B • Nivolumab (480 mg/dose IV every 4 weeks) for up to 92 weeks or until progression in follow-up-Cohort A and B • Nivolumab (480 mg/dose IV every 4 weeks) for up to 104 weeks or until progression in follow-up-Cohort C • Total of up to 104 weeks therapy- Cohort A, B, and C
Duration of Administration	Up to a total of 104 weeks of study treatment and 24 months of follow up in all Cohorts.
Statistical Methodology	A Mini-Max Simon Two-Stage design will be used to assess ORR defined as a 50% decline in PSA from baseline in CDK12 loss of function metastatic CRPC patients. It is assumed that an ORR of 30% or more would be interesting for further study compared to a reference ORR of 10% based on the KEYNOTE-199 trial [35] [1]. Accrual of 25 patients will provide 80% power to detect this difference in ORR with a type I error of 5%. Interim analysis will be completed after 15 patients (Cohort A only). If 2 or more patients have a PSA response, then the 2nd stage will open and accrue 10 more patients. If 6 or more patients out of 25 have a PSA response, then the treatment will be

	recommended for further study in this population. No interim analysis is planned for Cohort C. Cohort B will accrue 15 patients with non-prostate histology. A reference ORR of 5% is assumed in patients with non-prostate histology. With 15 patients, we have 76% power to detect an ORR of 25% with a one-sided type I error of 5%. If 3 or more responses are seen in cohort B, then we will conclude that there is preliminary evidence of activity. A total trial population of 65 subjects is planned.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Metastatic castrate-resistant prostate cancer (mCRPC) remains a challenging disease, with incremental resistance to multiple lines of therapy over time. However, greater understanding of the mutational landscape of mCRPC is providing more treatment options for advanced prostate cancer. Whole exome and transcriptome sequencing of a large multi-site cohort of patients with mCRPC performed by our group has identified several aberrations in DNA repair defect genes, including BRCA2, BRCA1, and ATM [1], and has provided the rationale for the clinical use of PARP inhibitors. However, one of the novel genomic aberrations in mCRPC demonstrated in our tumor genome sequencing initiative is the loss of CDK12 function [1] [2].

CDK12:

Relative prevalence of DNA-repair mutations in prostate cancer patients

	Localized PCa (%) [10,13]	Metastatic PCa (%) [15,16]
Homologous recombination pathway		
BRCA2	2–3	7–8
ATM	2–4	5–6
PALB2	<1	1–2
BRCA1	1	1
CHEK2	<1	1–2
RAD51	1–2	3–4
CDK12	1–2	5–6
Mismatch repair pathway		
MLH1	<1	1
MSH2	<1	2–3
MSH6	<1	1
PMS2	<1	<1
Overall	8–10	20–25

Figure 1 Tepley et al. Treatment strategies for DNA repair-deficient prostate cancer. Expert Rev Clin Pharmacol. 2017 Aug; 10(8):889-898.

Cyclin-dependent kinases (CDKs) have an important role in cell cycle regulation in conjunction with cyclin. Some cyclin-specific kinases function in gene transcription control, including CDK12 and CDK13, which are associated with cyclin K and have a role in regulating transcription elongation and RNA splicing. In an evaluation of CDK12 gene modification prevalence across various tumor types, there was a 1.08% mutation rate across 1203 prostate cancer samples, compared with 2.3% in 915 ovarian cancer samples [3]. In another recent analysis, the prevalence of CDK12 mutation in metastatic prostate cancer was found to be as high as 5-6%, as shown in Figure 1 [4]. Impairing CDK12 function in ovarian cancer cells decreases BCRA1 levels and disrupt homologous recombination repair, leading to reported increased sensitivity to cisplatin and PARP inhibition [5]. In addition to an association with non-functional homologous recombination (HR) repair, tumors with inactivated CDK12 have also demonstrated increased genomic instability. In a series of 556 ovarian carcinomas, 17 tumors were found to have markedly increased genomic copy number. 15 of these 17 cases also harbored CDK12 mutations,

the majority of which were deleterious [6]. Mutations in CDK12 are shown to cause downregulation of genes in the HR pathway, disabling repair of double-strand DNA breaks and leading to tumor genomic instability [7]. The work in the Michigan Center for Translational Pathology (MCTP) has recently identified a novel genetically unstable subset of prostate cancer typified by biallelic inactivation of CDK12. CDK12-mutants are genomically, transcriptionally, and phenotypically distinct from other DNA repair deficient subtypes such as mismatch repair (MMR) deficient tumors. CDK12 deficient CRPC tumors display a large number of gene fusions (Figure 1A, unpublished). Further, CDK12-mutant tumors exhibit a higher neoantigen burden than mCRPC in general (Figure 1B, unpublished). These attributes of the CDK12-mutant tumors could potentially be exploited clinically as tumor mutational burden and higher neoantigen load generally correlate with response to checkpoint inhibitor immunotherapy [8, 9].

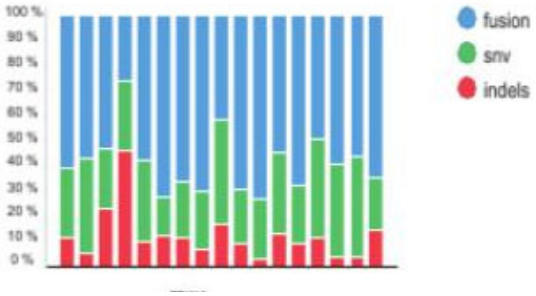


Fig. 1 A. Types of Genomic Aberrations in CDK12 mutant CRPC

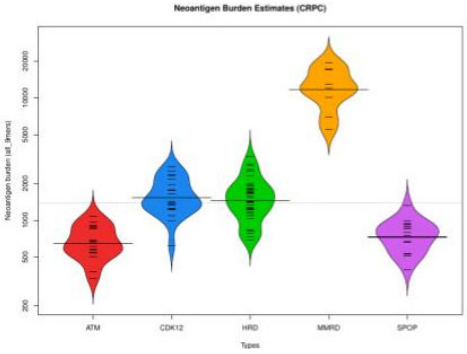


Fig. 1 B. Neoantigen load among various DNA defective CRPC tumors

MiOncoSeq-Directed Patient Selection:

To effectively conduct clinical studies targeting patients with CDK12 aberrations, rapid and accurate tumor sequencing to identify patients harboring this defect is needed. Dr. Chinnaiyan's lab has unparalleled expertise and experience for accomplishing this task, including on the Stand Up 2 Cancer (SU2C) East Coast Dream Team. The MCTP, which Dr. Chinnaiyan directs, also has extensive experience with correlative studies associated with tumor specimens and in the context of clinical trials. The Oncoseq1700 assay is a hybrid capture approach that currently interrogates 1733 genes in tumor DNA and germline DNA as well as RNA capture transcriptome of the tumor. Over 500X cover of the tumor and matched normal is achieved, and is compatible with formalin fixed or frozen samples obtained by soft tissue or bone biopsy. The Oncoseq assay is run in the MCTP's CLIA/CAP laboratory, with results provided as a report within 2-3 weeks. The Oncoseq approach can successfully identify sub-clones that comprise 2% or less of tumor cells as well as clinical biopsies with as little as 5% tumor content. By including whole RNA transcriptome analysis, we complement DNA-based mutational and copy number analyses with a functional read-out that highlights outlier expression and gene fusions. The composition of the 1733 gene panel begins with the 300-350 genes known to be recurrently mutated in a variety of cancers which form components of targeted cancer gene panels currently in use (e.g., FoundationOne). Our emphasis on sequencing matched normal allows the Oncoseq assay to make clear-cut germline calls which can often be useful to the family or have therapeutic implications (e.g., DNA repair gene defects and hypermutation/mismatch repair).

Immunotherapy in Prostate Cancer:

It has now been established that tumor mutational load and increased pathologic mutation rate correlate with a higher clinical benefit rate with cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade [8], and also correlate with prolonged overall survival with

immunotherapy [9]. In prostate cancer, however, prior studies evaluating the use of immunotherapy have been largely disappointing. In a phase I study of 39 patients treated with nivolumab anti-PD monotherapy, none of the 9 CRPC patients responded [10]. A recently published phase III study randomizing over 400 metastatic prostate cancer patients without visceral metastases to ipilimumab 10 mg/kg every 3 weeks versus placebo followed by maintenance therapy did not result in an overall survival benefit [11]. However, a recent phase II study showed early response to PDL-1 therapy in enzalutamide-resistant prostate cancer, with three of the first ten patients enrolled demonstrating rapid and deep PSA declines to ≤ 0.2 ng/ml. In one patient, this impressive response was associated with tumor microsatellite instability [12], and a similar response was reported in a patient with loss of function in MSH2 and MSH6 [13]. Aside from rare patients harboring mismatch repair mutations, there are some prostate cancer patients who have demonstrated response to immunotherapy where an underlying driver of response has not yet been identified. This inconsistent clinical response to immunotherapy suggests that the underlying tumor characteristics in prostate cancer that portend response to immunotherapy have not yet been identified. Clinically validated biomarkers for predicting response to immunotherapy have not yet been established, and greater understanding of additional drivers of response to these therapies in prostate cancer is urgently needed.
Combination therapy with ipilimumab and nivolumab has been used with success in the treatment of metastatic melanoma [14] and is now also being evaluated in small cell lung cancer [15]. Despite the potential for increased toxicities with a two-drug regimen, a recent meta-analysis evaluating immunotherapy in melanoma and lung cancer demonstrated improved PFS, OS, and ORR rates with combination therapy compared with monotherapy [16].

1.2 Study Agent(s) Background and Associated Known Toxicities

Nivolumab:

The clinical use of nivolumab, a fully human IgG4 monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and selectively inhibits PD-1 has been well-established across multiple cancer types. Through inhibition of the PD-1/PDL-1 interaction, immune pathway inhibition is therefore released, allowing increased T-cell activity against cancer cells. This drug has now been FDA approved in multiple disease types, including in unresectable or metastatic melanoma, metastatic non-small cell lung cancer, urothelial carcinoma, renal cell carcinoma.

Potential toxicities associated with the use of nivolumab immunotherapy have been well-established. The most common adverse reactions (in ≥20% of patients) with nivolumab as a single agent include fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. Most commonly documented adverse reactions of nivolumab in combination with ipilimumab include fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea.

Ipilimumab:

Clinical use of ipilimumab, a human CTLA-4-blocking antibody is approved for treatment of unresectable or metastatic melanoma and for adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes. Ipilimumab is approved at a dose of 3 mg/kg for unresectable or metastatic melanoma and at 10 mg/kg for adjuvant therapy in melanoma. The most common adverse reactions (in ≥5% of patients) are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia.

1.3 Rationale

In this study, we seek to assess the efficacy of immunotherapy in patients with CDK12 mutations in metastatic prostate cancer patients, and in other tumor histologies with CDK12 alterations. Increasing data has shown a correlation between response to immunotherapy and loss of normal DNA repair mechanisms [17] [18]. However, as previously discussed, CDK12 aberrations appear to be concordant with increased tumor genomic instability, suggesting a potentially robust response to immunotherapy not directly related to changes in DNA repair pathways. Combination immunotherapy has been shown to be associated with an improved response rate compared with single-agent therapy, and given the absence of identifiable benefit with ipilimumab monotherapy to date in prostate cancer, combination therapy with ipilimumab and nivolumab in a susceptible patient population may be associated with higher response rates. However, we hypothesize that CDK12 alterations would also result a baseline increased likelihood of response to immunotherapy. A robust treatment response with single-agent therapy may be seen in this highly selected population, while a therapeutic response was not previously captured in an unselected metastatic prostate cancer population.

We therefore propose a phase II study of nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy in patients with metastatic prostate cancer who have evidence of disease progression after at least one standard therapy (cohort A). Other advanced metastatic cancers with CDK12 changes, including ovarian cancer, would also be included (cohort B). Maintenance nivolumab at a flat dose of 480 mg IV given every 4 weeks will be continued until total protocol therapy of up to 104 weeks of therapy. Nivolumab at a flat dose of 480 mg IV given every 4 weeks will be continued until total protocol therapy of up to 104 weeks of therapy in Cohort C for prostate cancer patients.

1.4 Exploratory Studies

1.4.1 Mi-ONCOSEQ

We will sequence patients under our established Mi-ONCOSEQ [19] study, which is an effort to use integrative clinical sequencing towards personalized medicine for cancer patients. The matched tumor-normal library from WXS (whole exome sequencing) along with strand specific all-exon captured library from total RNA (captured transcriptome) will be sequenced at our CLIA certified sequencing laboratory.

1.4.2 Immune infiltration

To date, a definite correlation between response to immunotherapy and tumor cell or immune-infiltrating PD-L1 expression has not been established. We seek to profile immune infiltration in tumor biopsies in both patient cohorts.

2.0 STUDY OBJECTIVES/ENDPOINTS

2.1 Primary Objective

To determine the efficacy of checkpoint inhibitor immunotherapy, nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only, in patients with metastatic prostate cancer harboring loss of CDK12 function.

2.2 Secondary Objectives

2.2.1 To determine the efficacy of checkpoint inhibitor immunotherapy,nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or

nivolumab monotherapy only, in patients with metastatic non-prostate cancer harboring loss of CDK12 function.

2.2.2 To determine the safety and tolerability of nivolumab and ipilimumab combination, or nivolumab monotherapy only,therapy followed by nivolumab monotherapy in patients with metastatic cancers with loss of CDK12 function.

2.2.3 To evaluate other measures of clinical efficacy of checkpoint inhibitor immunotherapy in metastatic tumors with loss of CDK12 function.

2.2.4 To assess the Quality of Life (QoL) in subjects treated on protocol therapy.

2.3 Exploratory Objectives

2.3.1 To assess changes in the tumor genome with therapy.

2.3.2 To profile immune infiltration in tumor biopsies.

2.4 Primary Endpoint

The overall response rate (ORR) in subjects with metastatic castration resistant prostate cancer whose tumors harbor a genomic change resulting in CDK12 loss of function and who are treated with nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only (for applicable cohorts), as measured by PSA 50% decline from baseline as determined by PCWG3 criteria.

2.5 Secondary Endpoints

2.5.1 The overall response rate (ORR) in patients with metastatic non-prostate cancer harboring loss of CDK12 function, who are treated with nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only, as measured by RECIST 1.1 criteria.

2.5.2 The frequency and severity of adverse events, as assessed by CTCAE version 4.03 criteria, in patients with metastatic cancer harboring loss of CDK12 function treated with nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only,.

2.5.3 Assess the radiographic progression-free survival (rPFS), progression-free survival (PFS), duration of response (DOR) among responders, duration of therapy (DOT), time to progression (TTP), overall survival (OS) and objective tumor response in patients with measurable disease by RECIST 1.1 criteria. For subjects with metastatic CRPC, determine the PSA progression-free survival and time to PSA progression by PCWG3 criteria.

2.5.4 Measure the Quality of Life (QoL) in subjects treated on protocol therapy using EORTC-QLQ-C30 and BPI-SF.

2.6 Exploratory Endpoints

2.6.1 Tumor genome profiling by integrated DNA and RNA sequencing (including molecular tumor burden assessment) at baseline and optionally at progression.

2.6.2 Profiling of immune infiltration in tumor biopsies.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 Age ≥ 18 years and ability to understand and the willingness to sign a written informed consent.

3.1.2 ECOG Performance Status of 0, 1 or 2.

3.1.3 Subjects must have histologic or cytologic or radiologic evidence of metastatic adenocarcinoma of the prostate without small cell histology OR another type of metastatic carcinoma. Radiologic or pathologic evidence of metastases is allowed.

3.1.4 All subjects, regardless of cancer type, must have a documented CDK12 loss on a CLIA approved, Next Generation Sequencing assay (tissue, cell-free DNA or other is allowed) and is willing to provide archival tissue for analysis. CDK12 loss will be confirmed by the IND Sponsor (at the University of Michigan) and may include deleterious mutations (e.g truncating mutation, inactivating missense mutation), rearrangement or deletion. Because it is not always stated explicitly in all NGS platforms/assays, the Sponsor Investigator will determine which genomic aberrations constitute CDK12 loss. If tissue is unavailable, subject may still enroll.

3.1.5 Subjects with prostate cancer must have documented prostate cancer progression within six months prior to screening with PSA progression defined as a minimum of two rising PSA levels ≥ 1; at least one week between each assessment with a baseline PSA value at screening of ≥ 2 ng/mL, including after first generation anti-androgen withdrawal.

3.1.6 Subjects with prostate cancer must have ongoing androgen deprivation with total serum testosterone < 50 ng/dL (or < 0.50 ng/mL or 1.73 nmol/L)). If the subject is currently being treated with LHRH agonists (subjects who have not undergone an orchiectomy), this therapy must have been initiated at least 4 weeks prior to registration. This treatment must be continued throughout the study.

3.1.7 Subjects with non-prostate histologies must have RECIST 1.1-measurable cancer on computed tomography (CT) or magnetic resonance imaging (MRI) scans.

3.1.8 Subjects must have recovered to baseline or ≤ grade 1 CTCAE v 4.03 from toxicities related to any prior treatments unless AE(s) are clinically non-significant and/or stable.

3.1.9 Patients must be ≥ 2 weeks from most recent systemic therapy or most recent radiation therapy.

3.1.10 Women of childbearing potential must have a negative serum or urine pregnancy test within 28 days prior to registration. Women of non-childbearing potential are

defined as those who have no uterus, ligation of the fallopian tubes, are naturally postmenopausal for at least 12 consecutive months or have undergone surgical removal of the ovaries.

3.1.11 Female and male subjects of reproductive potential must agree to use an adequate method of contraception starting with the first dose of study therapy through 5 months (for women) and 7 months (for men) after the last dose of study therapy.

3.1.12 Adequate organ and marrow function as defined below:

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1,000/mm^3
Hemoglobin (Hgb)	≥ 8 g/dL with or without pRBC transfusion
Platelets (Plt)	≥ 100,000/mm^3
Renal	
Calculated or measured creatinine clearance	Serum creatinine <3.0 mg/dl or if elevated, a calculated estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2.
Hepatic	
Total Bilirubin	≤ 2.5 × upper limit of normal (ULN) (patients with known Gilbert disease who have serum bilirubin ≤3x ULN may be enrolled)
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN

3.2 Exclusion Criteria

3.2.1 Prior treatment with anti-PD-1/PD-L1 and anti-CTLA-4 is NOT allowed. Prior intravesical BCG therapy is allowed.

3.2.2 Treatment with any investigational agent or on an interventional clinical trial within 28 days prior to registration on this protocol.

3.2.3 Prior or concurrent malignancy that has needed active interventional systemic therapy in the last 2 years. Adequately treated basal cell or squamous cell skin cancer, non muscle-invasive urothelial cancer, in situ cervical cancer, are permitted. For subjects in the non-prostate cancer cohort, localized or locally advanced prostate cancer definitively treated without recurrence or with biochemical recurrence only, or any other cancer fully treated or from which the subject has been disease-free for at least 2 years.

3.2.4 History or risk of any of the following significant autoimmune diseases are excluded, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bells' palsy, Guillain-Barre syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. Vitiligo, mild psoriasis (topical therapy only) or hypothyroidism are allowed. No prior history of autoimmune pneumonitis allowed. Patients with previous drug-related or radiation therapy-associated pneumonitis, or other forms of pneumonitis, that has since resolved are allowed.

3.2.5 Need for systemic corticosteroids > 10mg prednisone daily or equivalent alternative steroid (except physiologic dose for adrenal replacement therapy) or other immunosuppressive agents (such as cyclosporine or methotrexate). Topical and inhaled corticosteroids are allowed if medically needed.

3.2.6 Any history of organ allografts.

3.2.7 Must not have known active hepatitis B, hepatitis C, or HIV seropositivity. Negative PCR suggests infection is not active or latent; however testing is not required in the absence of clinical suspicion.

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Patient registration for this trial will be centrally managed by the Coordinating Center of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on a Screening and Enrollment Log.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

The Multi-Site Coordinator (MSC) of the Coordinating Center will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the MSC to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the MSC, will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in a Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 14 business days of enrollment to the study.

5.1.1 In this study, Cohort A and Cohort B patients will start treatment with nivolumab dosed at 3 mg/kg IV and ipilimumab 1 mg/kg every 3 weeks for up to 4 doses. Cohort C patients will receive immunotherapy with nivolumab dosed at a flat dose of 480 mg IV every 4 weeks for up to 26 doses or 104 weeks.

5.1.2. Cohorts A and B maintenance immunotherapy with nivolumab dosed at a flat dose of 480 mg IV every 4 weeks will be continued for up to 23 doses or 92 weeks. Missed doses of 480 mg Nivolumab due to toxicity or general health condition will be skipped.

5.1.3 Total protocol therapy for all Cohorts will be up to 104 weeks during treatment. If disease progression or recurrence occurs during the follow-up phase, then per treating physician discretion, the patient may resume nivolumab 480 mg IV every 4 weeks until progression if tolerated with axial imaging as per protocol every, 12 weeks.

5.1.4 All study therapy will be administered on an outpatient basis.

Agent	Precautions	Dose	Route	Schedule	Cycle Length
Nivolumab (solution for injection) induction Cohort A and B only	Administer before other immunotherapy agents	3 mg/kg up to 4 doses	IV infusion over 30 minutes, +/- 10 minutes, with a sterile, nonpyrogenic, low protein binding 0.2 to 1.2 micrometer in-line filter. Follow with saline flush.	Day 1	3 weeks
Ipilimumab (solution for injection) induction Cohort A and B only	Administer 30 minutes after nivolumab.	1 mg/kg up to 4 doses	IV infusion over 90 minutes, +/- 10 minutes, through a non-pyrogenic, low protein-binding in-line filter. Separate IV line required.	Day 1	3 weeks
Nivolumab (solution for injection) maintenance After induction in Cohorts A and B; and throughout in Cohort C	Administer before other immunotherapy agents	480 mg up to 23 doses (92 weeks in Cohort A and B, and 104 weeks in Cohort C)	IV infusion over 30 minutes, +/- 10 minutes, with a sterile, nonpyrogenic, low protein binding 0.2 to 1.2 micrometer in-line filter. Follow with saline flush.	Day 1	4 weeks

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.1). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Dose changes of either study drug is NOT permitted. Doses can be held however as necessary. Dosing holds should be made according to the system showing the greatest degree of toxicity.

Adverse Event Related vs Unrelated Dose Delays: If dose delay is due to an unrelated Adverse Event then reason for hold must be documented. Any patient on this protocol will be allowed to continue to receive study treatment at the investigator's discretion, regardless of AE relatedness. Do not have to delay dose for unrelated Adverse Event.

5.2.1 Treatment delay for toxicity of more than 84 days from last intended therapy will result in treatment discontinuation for the specific drug(s) responsible for the toxicity. If ipilimumab is permanently discontinued, then discontinue Nivolumab 3mg/kg. Nivolumab 480 mg can be continued.

5.2.2 Investigators should consider dose re-calculation of ipilimumab with change in weight as per standard of care/institutional guidelines. However, a change in weight by 10% or more should lead to a dose re-calculation.

5.2.3 Nivolumab and/or ipilimumab cannot be dose reduced in response to toxicity, and can only be held or discontinued as per detailed algorithms for immune-therapy toxicity management below.

NCI CTCAE v 4 Grade	Nivolumab	Ipilimumab
0-1	No change from original starting dose	No change from original starting dose
2	Withhold drug, resume treatment when adverse reaction improves to grade 0 or 1	Withhold drug, resume treatment when adverse reaction improves to grade 0 or 1
3	Withhold drug, resume treatment when adverse reaction improves to grade 0 or 1 when given as a single agent	Withhold drug, resume treatment when adverse reaction improves to grade 0 or 1
Second episode of grade 3 or any episode of grade 4 toxicity	Permanently discontinue therapy and remove subject from trial	Permanently discontinue therapy and remove subject from trial

Certain adverse events that are possibly immune mediated warrant special monitoring and management, and are outline below to guide investigators.

5.2.4.1 Pulmonary:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Evaluate with imaging and pulmonary consultation.

Grade of pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay nivolumab or ipilimumab • Monitor for symptoms every 2-3 days • Consider pulmonary and infectious disease consultations	• Re-image at least every 3 weeks If worsens: If worsens: • Treat as Grade 2 or 3-4

Grade 2 Mild to moderate new symptoms	• Delay nivolumab or ipilimumab • Consult pulmonary and infectious disease • Monitor symptoms daily, consider hospitalization • 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider bronchoscopy and/or lung biopsy	• Re-image every 1-3 days If improves:If improves: • When symptoms return to near baseline, taper steroids over at least one month and resume nivolumab and ipilimumab per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4 If not improving after 2 weeks or worsening, treat as grade 3 or 4
Grade 3 or 4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue nivolumab or ipilimumab • Hospitalize • Consult pulmonary and infectious disease • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy and/or lung biopsy	If improves to baseline: • Taper steroids over 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

5.2.4.2 Gastrointestinal:
Rule out non-inflammatory causes. If non-inflammatory is identified, treat accordingly and continue protocol theraphy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in case of perforation or sepsis.

Grade of diarrhea/colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue nivolumab or ipilimumab per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL	• Delay nivolumab and ipilimumab per protocol • Symptomatic treatment	If improves to grade 1: Resume nivolumab or ipilimumab per protocol If persists > 5-7 days or recur:

Grade of diarrhea/colitis (NCI CTCAE v4)	Management	Follow-up
Colitis: abdominal pain; blood in stool		• 0.5-1.0mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibotics for opportunistic infections, and resume nivolumab or ipilimumab per protocol If worsens or persists > 3-5 day with oral steroids: • Treat grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue nivolumab or ipilimumab per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

5.2.4.3 Endocrinopathy:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider visual field testing, endocrinology consultation and imaging.

Endocrinopathy	Management	Follow-up
Asymptomatic thyroid-stimulating hormone (TSH) elevation	• Continue nivolumab or ipilimumab • If TSH <0.5 x LLN, or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cyles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	• Evaluate endocrine function • Consider pituitary scan <u>Symptomatic with abnormal lab/pituitary scan:</u> • Delay study therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent • Initiate appropriate hormone therapy <u>No abnormal lab/pituitary MRI scan but symptoms persist:</u> • Repeat labs in 1-3 weeks / MRI in 1 month	<u>If improves (with or without hormone replacement):</u> • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume protocol therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness	• Delay or discontinue nivolumab or ipilimumab per protocol Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity IV fluids • Consult endocrinologist • If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

5.2.4.4 Hepatic:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3 x ULN and/or total bilirubin > ULN to 1.5 x ULN	• Continue nivolumab or ipilimumab	• Continue liver function test (LFT) per protocol <u>If worsening:</u> • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > ULN to 1.5-to ≤ 3 x ULN	• Delay nivolumab or ipilimumab per protocol • Increase frequency of monitoring to every 3 days	<u>If returns to baseline:</u> • Resume routine monitoring, resume nivolumab or ipilimumab <u>If persists > 5-7 days or worsens</u>: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab and ipilimumab
Grade 3 or 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	• Discontinue nivolumab or ipilimumab* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infection • Consult gastroenterologist	<u>If returns to grade 2:</u> • Taper steroids over at least one month <u>If does not improve in > 3-5 days, worsens or rebounds:</u> • Add mycophenolate mofetil 1g twice daily • If no response within an additional 3-5 days, consider other immunosuppressive agents per local guidelines

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

5.2.4.5 Neurological:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.

Grade of neurological toxicity (NCI CTCAE v 4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; intervention not indicated	• Continue nivolumab or ipilimumab	• Continue to monitor the patient. If worsens:. • Treat as grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay nivolumab or ipilimumab • Treat symptoms per institutional guidelines • Consider 0.5-1mg/kg per day methylprednisolone IV or oral equivalent	If returns to baseline: • Resume nivolumab or ipilimumab If worsens: • Treat as Grade 3 - 4
Grade 3 or 4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue nivolumab or ipilimumab • Consult Neurology • Treat symptoms per institutional guidelines • 1-2mg/kg per day IV methylprednisolone or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to grade 2: • Taper steroids over at least one month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per institutional guidelines

5.2.4.6 Skin:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 Covering ≤ 30% body surface area (BSA)*	• Symptomatic therapy (e.g. antihistamines, topical steroids) • Continue nivolumab or ipilimumab	If persists > 1-2 weeks or recurs: • Consider skin biopsy • Delay nivolumab or ipilimumab • Consider 0.5-1mg/kg/day methylprednisolone IV or oral equivalent. Once improving , taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab or ipilimumab If worsens: Treat as Grade 3-4

Grade 3-4 Covering >30% BSA; or life threatening consequences*^	• Delay or discontinue nivolumab or ipilimumab • Consider skin biopsy • Consult dermatology • 1-2mg/kg/day methylprednisolone IV or IV equivalent	<u>If improves to grade 1:</u> • Taper steroids over at least one month and add prophylactic antibiotics for opportunisitic infections • Resume nivolumab or ipilimumab

*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue nivolumab and ipilimumab

5.2.4.7 Renal:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy

Grade of elevation in serum creatinine (NCI CTCAE v4)	Management	Follow-up
Grade 1 Serum creatinine > ULN and > than baseline but ≤ 1.5 x baseline	• Continue nivolumab /or ipilimumab • Monitor serum creatinine weekly	<u>If returns to baseline</u>: • Resume creatinine monitoring per protocol <u>If worsens:</u> • Treat as Grade 2, 3/4
Grade 2-3 Serum creatinine > 1.5 x baseline to ≤ 6 x ULN	• Delay nivolumab or ipilimumab • Monitor serum creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> Taper steroids over at least 1 month, consider prophylactic antibotics for opportunistic infections, and resume nivolumab and ipilimumab and routine serum creatine monitoring per protocol <u>If elevations persists > 7days or worsen:</u> • Treat as Grade 4
Grade 4 Serum creatinine > 6 x ULN	• Discontinue nivolumab or ipilimumab • Monitor serum creatinine daily • 1-2mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrology • Consult renal biopsy	<u>If returns to Grade 1:</u> • Taper steroids over at least one month and add prophylactic antiobotics for opportunistic infections

5.2.4.8 Myocarditis:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy

Grade of Rash Myocarditis (NCI CTCAE v4)	Management	Follow-up
Grade 2 Symptoms with mild to moderate activity or exertion	• Delay nivolumab or ipilimumab hospitalization with cardiac monitoring • Urgent cardiology consultation for evaluation and management o Troponin and BNP o ECG ±continuous cardia monitoring o Echocardiogram o Cardiac MRI • Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent	• If worsens, intensify treatment according to grade • Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms • Repeat cardiac MRI for post treatment assessment and cardiology follow-up • Retreatment may be considered after recovery and completion of steroid taper
Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated **Grade 4:** Life threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	• Permanently discontinue nivolumab or ipilimumab • Hospitalize to intensive cardiac monitoring o Cardiac evaluation to include: o Troponin and BNP monitoringECG ± continuous cardic monitoring o Echocardiogram o Cardiac MRI o Myocardial biopsy if feasible • Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus • Consider adding a second immunosuppressive agent Additionally, for Grade 4: • Hospitalize/transfer to institution with expertise in intensive cardiac monitoring • Consider ATG as second agent given its immediate effect	• If no improvement, consider additional immunosuppression • Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms • Repeat cardiac MRI for post treatmentassessments and cardiology follow-up

5.2.4.9 Ocular manifestations:
Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving ipilimumab and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

5.2.4.10 Other:
For rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued, and appropriate treatment instituted.

5.3 Concomitant Medications/Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Study PI. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor-Investigator and the subject.

Use of bisphosphonates/RANKL inhibitors are standard in CRPC and are allowed on the study. Starting bisphosphonates if indicated is allowed while on study.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy except for ongoing androgen deprivation therapy (e.g. with LHRH agonist/antagonist)
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than checkpoint inhibitor immunotherapy
- 5 α-reductase inhibitors (e.g., finasteride, dutasteride)
- Any herbal product known to decrease PSA levels (e.g. Saw Palmetto and PC-SPES)
- Neulasta®
- Radiation therapy
- Local intervention is discouraged unless medically unavoidable. Radiation therapy to a symptomatic solitary lesion/area may be considered on a case-by-case basis after consultation with the Principal Investigator (except during screening). Subjects receiving local intervention (e.g., palliative radiation) are allowed to continue to receive study treatment at the investigator’s discretion. Subjects who receive local intervention may be considered not evaluable (and may be assigned a conservative censoring or progression date).
- Live vaccines within 30 days prior registration and while participating the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, intranasal influenza, rabies, BCG (tuberculosis vaccine), and typhoid vaccine. If precluded by local regulations, live vaccines should not be given for 120 days after the last dose of checkpoint inhibitor immunotherapy is administered.
- Systemic glucocorticoids or other immunosuppressive drugs for any purpose other than to modulate symptoms from a drug-related AE of immunologic etiology (refer to Section 5.2 –

Dose Modification). The use of physiologic doses of corticosteroids may be approved after consultation with the Study PI.

- Use of prophylactic corticosteroids to avoid allergic and other adverse reactions (e.g., to IV contrast dye or transfusions) is permitted.

- Use of intermittent inhaled steroids or local injection of corticosteroids into joints is permitted upon consultation with the Study PI.

- Physiologic doses of prednisone ≤10 mg (or equivalent) per day.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for a total of 104 weeks in all from the start of study therapy or until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Do not hold scans, continue scan schedule every 12 weeks from cycle 5 day 1 regardless of treatment delays thereafter.

5.5 Off Treatment Criteria

Patients will be removed from protocol specified therapy when any of the criteria listed in Section 5.4 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.6 Duration of Follow-Up

Patients will be followed every 3 months for 24 months after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.7 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study or study drug therapy will be documented and may include:

5.7.1 Patient withdraws consent (termination of treatment and follow-up);

5.7.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

5.7.3 Patient is unable to comply with protocol requirements;

5.7.4 Treating physician determines continuation on the study would not be in the patient's best interest;

5.7.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event); study patient will undergo the EOT visit and follow-up visits excluding tumor biopsy according to the activities in this protocol and study procedure assessments.

5.7.6 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.7.7 Lost to Follow-up;

5.7.8 Termination of the study by The University of Michigan;

5.7.9 Patient completes protocol treatment and follow-up criteria.

5.8 Patient Replacement

Patients who do not receive any dose of the study drug will be replaced.

6.0 STUDY PROCEDURES

6.1 SCHEDULE OF ASSESSMENTS:

	Screening (within 28 days)	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**D1C5+**	**EOT[12]**	**Follow Up[8]**
Informed Consent	X							
Review Eligibility Criteria	X							
Demographics, Height	X							
Prior and Concomitant Medications	X	X	X	X	X	X	X	
Review Adverse Events[10]	X	X	X	X	X	X	X	
Physical Examination, Vital Signs[1], Weight	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	
Survival Status								X Q3m
Laboratory Assessments								
Pregnancy Test for WOBCP[2]	X							
CBC with diff, platelets[3]	X	X	X	X	X	X	X	
Comprehensive Metabolic Panel, including Alk Phos[4]	X	X	X	X	X	X	X	

	Screening (within 28 days)	C1D1	C2D1	C3D1	C4D1	D1C5+	EOT[12]	Follow Up[8]
LDH	X	X	X	X	X			
PSA[11]	X	X	X	X	X	X	X	X
Testosterone[11]	X				X		X	
TSH, free T3, free T4 (If Clinically Indicated: FSH, LH, ACTH)	X	X	X	X	X	X[6]	X	
Therapy								
Cohorts A and B Nivolumab 3 mg/kg IV q3 wks for up to 4 doses[13]		X						
Cohorts A and B Ipilimumab 1 mg/kg IV q3 wks for up to 4 doses[13]		X						
Cohorts A and B Nivolumab 480 mg IV q4 wks for up to 23 doses[13]						X		
Cohort C Nivolumab 480 mg IV q4 wks[14]		X				X		
Imaging Tumor Assessments								
CT chest	X					X (q 12 wks)		
CT Abdomen/Pelvis or MRI Abdomen/Pelvis [5]	X					X (q 12 wks)		
$Tc^{99}m$ Bone Scan (prostate only)	X					X (q 12 wks)		
QoL: BPI-SF and EORTC QLQ C30	X					X (q 12 wks)		
Correlatives								
Tumor Tissue Archival (CRPC preferred if available)	X							
Tumor Biopsy	X						X[7]	
Research blood [9]		X	X	X		X (q 12 wks)	X	

1. Vital signs will include temperature, pulse, respirations, blood pressure; height will be obtained at screening only.
2. WOCBP: Women of child bearing potential; urine or serum pregnancy test.
3. CBC with diff includes total WBC, hemoglobin, hematocrit and differential of the WBC including absolute counts.
4. COMP or Comprehensive metabolic profile includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin.
5. With or without intravenous contrast, before or on associated visit. CT or MRI (preferred) brain with or without IV contrast if suspected or known brain metastases. Frequency of tumor assessments will be q12 weeks.
6. Every 42 calendar days ± 14 business days. May be delayed if infusion is not scheduled within the window.
7. Optional tissue biopsy collection at progression if subject consents; +/- 14 working days.
8. Follow up with phone call or with clinic visit.
9. Blood for research should be collected prior to study treatment on C1D1, C2D1, C3D1 and C5D1, every 12 weeks thereafter and end of treatment.

10. Data on adverse events will be collected from the time of the initial study drug administration through 100 days after the last dose of study drug (nivolumab and/or ipilimumab) as described in Section 8.2.
11. For Cohort A only
12. End of Treatment Visit should occur within 3-4 weeks of last dose of protocol therapy.
13. Cohorts A and B (Nivolumab and Ipilimumab: 1 cycle (C) = 21 days (D) for up to 4 doses of Nivolumab (3mg/kg IV) and Ipilimumab (1mg/kg IV), then Nivolumab maintenance therapy alone (480mg IV): 1 cycle=4 weeks or 28 days (D). Total treatment time is up to 104 weeks.
14. Cohort C (Nivolumab monotherapy): 1 cycle (C) = 28 days (D) of Nivolumab monotherapy (480mg IV) for up to 104 weeks.

NOTE:
All procedures in study assessments schedule have a window of ± 3 business days unless otherwise mentioned. Virtual clinic visits will be allowed per clinician/ subject discretion.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Prostate Cancer

While on therapy with either nivolumab alone or in combination with ipilimumab, patients with mCPRC will undergo laboratory monitoring on day 1 of each treatment cycle, including PSA, repeated every 4 weeks.

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for Objective PSA Response. All patients enrolled in Cohort A who received at least 1 cycle(s) of therapy, and who have 2 PSA measurements after protocol therapy initiation will be considered evaluable for PSA response. Patients who exhibit objective or clinical disease progression prior to collection of 2 PSA measurements will also be considered evaluable.

7.1.1 PSA Response Rate

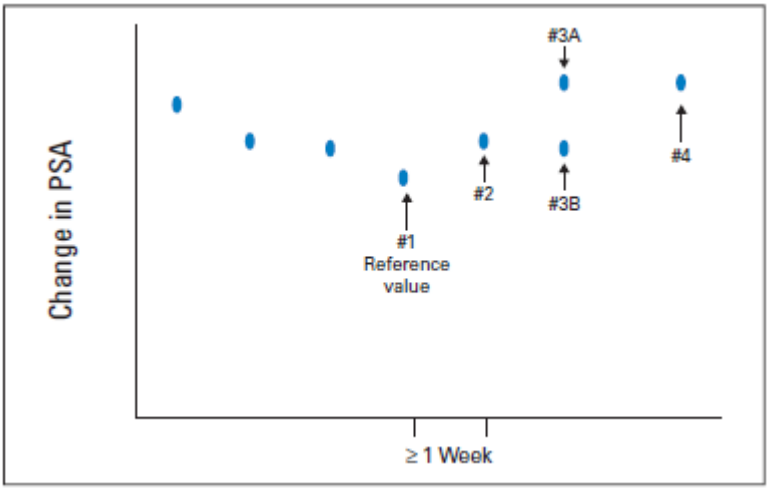
Per PCWG3 criteria, PSA response rate will be defined as the proportion of subjects who have PSA response as defined by at least 50% decline in PSA level from baseline measured twice at least 3 weeks apart. Based on the PCWG3 criteria, a favorable effect on PSA may be delayed for ≥ 12 weeks. PSA will be monitored every 4 weeks, but treatment will be planned to continue through early rises for 12 weeks unless other evidence of progression, such as radiographic progression.

Therefore, early rises in PSA before 12 weeks will not be considered when determining PSA response.

7.1.2 Criteria for PSA Progression

For rising PSA after an initial decline from baseline, the PSA is recorded from the start of therapy to first PSA increase that is ≥ 25% and ≥ 2ng/mL above the nadir, which is confirmed by a second value 4 or more weeks later, confirming a rising trend. If there is no initial decline from baseline, PSA progression is defined as ≥ 25% increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks.

Patients who have only documented PSA progression in the absence of radiographic or clinical progression may continue on study therapy.



7.1.3 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for PSA response until the first date that PSA progression is documented, or if there is interval development of recurrent or progressive disease objectively documented by RECIST 1.1 criteria.

7.1.4 Progression-Free Survival

PSA progression-free survival (PSA-PFS) is defined as the duration of time from start of treatment to time of PSA progression as defined above in section 7.1.2 or death, the event that occurs first. Patients who have not experienced either event at the time of analysis will be censored at the last PSA measurement date.

Radiographic progression-free survival (rPFS) is defined as the duration of time from start of treatment to time of radiographic progression as defined above in section 7.1.5 or death, the event that occurs first. Patients who have not experienced either event at the time of analysis will be censored at their last radiographic scan date.

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of first PCWG3 defined progression or death, the event that occurs first. Patients who have not experienced either event at the time of analysis will be censored at the date of their last progression assessment.

7.1.5 Radiographic Response Criteria

All radiographic response criteria are as per PCWG3 criteria summarized below.

7.1.5.1 Nodal Disease

Up to five (5) lesions are recorded per site of disease. These will be assessed as per RECIST 1.1 with the following PCWG3 caveats:

1. Changes in size are recorded using a waterfall plot
2. Favorable change is confirmed with a second scan
3. Complete elimination of disease at any site is recorded separately

4. Only changes in lymph nodes that were ≥1.5 cm in the short axis are reported
5. Changes in pelvic (regional) nodes versus extrapelvic (distant/metastatic) nodes are recorded separately

7.1.5.2 Visceral Disease

Visceral disease includes lesions in lung, liver, adrenal, and CNS sites. These will be assessed as per RECIST 1.1 with the following PCWG3 caveats:

1. Changes in liver, lung, adrenal, and CNS sites are recorded separately.
2. Only changes in lesions ≥1.0 cm in the longest dimension are reported

7.1.5.3 Bone Disease

Bone disease is evaluated as per PCWG3 criteria, with changes recorded as improved or stable (no new lesions) or worse (new lesions). Additional PCWG3 caveats include:

1. Changes in intensity of uptake alone do not constitute progression or regression
2. No new lesions: continue therapy in absence of other signs of progression
3. New lesions (progression) is defined by the following per PCWG3:
    a. Exclude pseudoprogression in the absence of symptoms or other signs of progression
    b. At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)
    c. If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented
    d. For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan

7.2 Antitumor Effect- Non-Prostate Malignancies

(For Cohort B only)

For patients with metastatic non-prostate cancer and measurable disease, response and progression will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [34]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

Immunotherapy drugs such as nivolumab and ipilimumab can initially cause inflammation in the early stages of treatment. Immune-related RECIST (irRECIST) utilizes RECISTv1.1 but considers an inflammatory response (or “pseudo-progression”) as normal. The main difference between RECISTv1.1 and irRECIST is that patients can stay on trial after the first progressive disease (PD) assessment (as per RECISTv1.1) if using immune-related

RECIST criteria. This PD per RECISTv1.1 is then re-labeled as immune related stable disease (irSD) per irRECIST and requires addition of unidimensional measurements of all new lesions (that meet the definition of target lesion) to be added to the sum of longest diameters (SLD) calculation for response assessment. Importantly, immune-related progression (irPD) must be confirmed by a follow-up scan at least 4 weeks (within 4-8 weeks) following the initial PD/irSD assessment in order to take the patient off the trial.

Subjects that are deemed to have clinical progression and unstable should not be continued on therapy after PD (per RECISTv1.1) and are therefore not required to have repeat tumor imaging for confirmation as per irPD definition. It is at the discretion of the site investigator whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects treated will be permitted to continue study treatment beyond initial RECISTv1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator determined clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

A radiographic assessment/ scan should be performed within 4-8 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD (termed irPD). The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.
If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Study Calendar (see Section 6.1).

Immune-related Progressive Disease (irPD): For the subjects who continue study therapy beyond progression, further progression is defined as an additional 20% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD, unequivocal worsening of NT lesions, or appearance of new lesions since the last evaluation. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression (i.e. irPD).

7.2.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response. All patients enrolled who received at least 1 cycle(s) of therapy, and who have measurable disease present at baseline and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective or clinical disease progression prior to the end of cycle 1 will also be considered evaluable.)

7.2.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be record as non-measurable)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Note: Tumor lesions that are situated in a previously irradiated area will only be considered measurable if they have had subsequent progression by at least 5mm.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions without measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (non-nodal lesions with the longest diameter), be representative of all involved organ(s), but in addition should be those that lend themselves to reproducible repeated measurements. If a non-nodal lesion is either not present or is initially measured with longest diameter <10mm as a non-target then grows to >10mm after baseline, this lesion then becomes a new target lesion as per irRECIST criteria. The non-nodal longest diameter is then added to the sum of diameters, and patient response is calculated with the new lesion.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is

the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If a non-target lymph node grows to >15mm after baseline, this node then becomes a new target lesion as per irRECIST. The nodal short axis is then added to the sum of diameters, and patient response is calculated with the new lesion.

Non-target lesions. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

7.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion

should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

7.4 Response Criteria

7.4.1 Evaluation of Target Lesions

Prior to the first PD assessment, patients will be evaluated according the following RECISTv1.1 response:

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

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

For Cohort B only: After the first PD assessment per RECISTv1.1 (=irSD per irRECIST), patients will be evaluated for irPD at least 4 weeks apart according to the following definition:

Immune-related Progressive Disease (irPD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of

5 mm), taking as reference the smallest sum LD recorded since the treatment started, or appearance of new lesions since the last evaluation.

7.4.2 Evaluation of Non-Target Lesions

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression on non-target lesions in absence of stable target lesions is exceptional, the opinion of the treating physician should prevail in such circumstances.

7.4.3 Evaluation of Best Overall Response

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

Evaluation as per RECISTv1.1 and irRECIST.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response per RECIST 1.1	Overall Response per irRECIST *(Cohort B only)*	Best Response for this Category Also Requires:
CR	CR	No	CR	N/A	≥4 wks. confirmation
CR	CR Non-CR/SD	No	PR	N/A	≥4 wks. confirmation
PR	CR Non-CR/PD	No			
SD	CR Non-CR/PD	No	SD	N/A	documented at least once ≥4 wks. from baseline
PD	Any	Any	PD	irSD	≥4 wks. from baseline;
Any	PD*	Any			
Any	Any	Yes			
PD	Any	Any	N/A	irPD	No further confirmation required
Any	PD*	Any			
Any	Any	Yes			

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

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

N/A=not applicable

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery

7.5 Duration of Response - Non prostate malignancies

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

7.6 Progression-Free Survival - Non prostate malignancies

Radiographic progression-free survival (PFS) is defined as the duration of time from start of treatment to time of radiographic progression as defined above in section 7.4 or death, the event that occurs first. Patients who have not experienced either event at the time of analysis will be censored at their last radiographic scan date.

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of radiographic or clinical progression or death, the event that occurs first. Patients who have not experienced either event at the time of analysis will be censored at the date of their last progression assessment.

7.7 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html)).

8.0 ADVERSE EVENTS

8.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

Special Warnings and Precautions for Use

Subjects receiving nivolumab and/or ipilimumab are advised to use two acceptable (to treating investigator) methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of informed consent and continuing

throughout the course of treatment and for at least 5 months (for women) and 7 months (for men) after nivolumab and/or ipilimumab immunotherapy is discontinued.

8.2 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study drug administration through 100 days after the last dose of study drug, that is nivolumab and/or ipilimumab. Any serious adverse event that occurs more than 100 days after the last study drug dose and is considered related to the study drug must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study drug, nivolumab and/or ipilimumab, for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration through 100 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

8.3 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- *Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.*

- *Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.*

Serious Adverse Event

An adverse event is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.

- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in the protocol, or in the informed consent document.

8.4 Adverse Event Characteristics

8.4.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.4.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

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

8.5 Serious Adverse Event Reporting Guidelines

8.5.1 Reporting procedures for multi-site trials

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center SAE form as available in the study database. A copy of the Coordinating Center SAE form as available in the study database should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

Participating sites should report all SAEs and UPs to their local IRB per current local institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or 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 drug. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

8.5.2 Reporting procedures to BMS

All Serious Adverse Events (SAEs) occurring from the initial study treatment administration through 100 days following the last dose of the study treatment will

be reported by the Coordinating Center to BMS Worldwide safety. Any SAEs occurring after 100 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to BMS Worldwide safety.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to BMS Worldwide Safety (Worldwide.Safety@bms.com; Fax: 609-818-3804).

If only limited information is initially available or an ongoing SAE changes in its intensity or relationship to the study drug, or if new information becomes available, a follow-up report will be generated and sent to BMS Worldwide Safety within 24 hours of receipt.

8.5.3 Reporting procedures to FDA

In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A Form. The Michigan IND/IDE Assistance Program (MIAP) (University of Michigan) will assist the IND Sponsor in reporting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32. This reporting could include the initial report and follow-up reports when appropriate for the event.

8.6 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 7 calendar days of the study team becoming aware of the problem.

8.8 Safety Report Reconciliation

The Sponsor will reconcile the clinical database SAE reports transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E

will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for identification purposes. If the Investigator determines a report was not transmitted to BMS GPV&E, the report should be sent immediately to BMS.

9.0 DRUG INFORMATION

9.1 Nivolumab

- Other names for the drug: Opdivo

- Description: Injection: 100 mg/10 mL solution in a single-dose vial.

- Classification - type of agent: Immunomodulatory; checkpoint inhibitor

- Mode of action:
  Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.
  Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

- Pharmacokinetics:
  Nivolumab pharmacokinetics (PK) were assessed using a population PK approach for both single-agent nivolumab and nivolumab with ipilimumab.
  nivolumab as a single agent: The PK of single-agent was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

  Nivolumab with ipilimumab: The geometric mean (CV%) CL, Vss, and terminal halflife of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When administered in combination, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

- Side effects:
  Nivolumab as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea,

nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia.
Nivolumab with ipilimumab: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea.

- Drug Interactions:
  No formal pharmacokinetic drug-drug interaction studies have been conducted with nivolumab.

- Storage and stability:
  The product does not contain a preservative. After preparation, store the nivolumab infusion either:
  • at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
  • under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation. Do not freeze.

- Preparation and Dispensing:
  Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.
  • Withdraw the required volume of nivolumab and transfer into an intravenous container.
  • Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
  • Mix diluted solution by gentle inversion. Do not shake.
  • Discard partially used vials or empty vials of nivolumab.

- Administration:
  Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion.
  When administered in combination with ipilimumab, infuse nivolumab first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

- Availability**:** Provided by Bristol Myers Squibb, Inc.
- Return and Retention of Study Drug:
- Handling and disposal of nivolumab should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents

- Drug Accountability:
- The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of nivolumab. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

9.2 Ipilimumab

- Other names for the drug: Yervoy

- Description:

  Injection: 200 mg/40 mL (5 mg/mL) (3)

- Classification - type of agent: Immunomodulatory; checkpoint inhibitor

- Mode of action: human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody

- Pharmacokinetics:
  The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 to 10 mg/kg. Following administration of ipilimumab every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean Cmin at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks. The mean value (percent coefficient of variation) based on population PK analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%). Specific Populations The effects of various covariates on the PK of ipilimumab were assessed in population PK analyses. The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment, mild hepatic impairment, previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-Caucasian ethnic groups.

  Renal Impairment: No clinically important differences in the CL of ipilimumab were found between patients with renal impairment and patients with normal renal function.

  Hepatic Impairment: The effect of hepatic impairment on the CL of ipilimumab was evaluated in patients with mild hepatic impairment (n=76) compared to patients with normal hepatic function (n=708) in the population PK analyses, and no clinically important differences in the CL of ipilimumab were found. Ipilimumab has not been studied in patients with moderate or severe hepatic impairment.

- Side effects: Ipilimumab can result in severe and fatal immune-mediated reactions.

- Drug Interactions: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab.

- Storage and stability:
  • Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).

- Preparation and Dispensing:
  • Do not shake product.
  • Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.
  • Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
  • Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
  • Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to

prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
• Discard partially used vials or empty vials of ipilimumab.

- Administration:
  • Do not mix ipilimumab with, or administer as an infusion with, other medicinal products.
  • Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
  • Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

- Availability**:** Provided by Bristol Myers Squibb, Inc.

- Return and Retention of Study Drug:Handling and disposal of ipilimumab should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents

- Drug Accountability:The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of ipilimumab. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

10.0 CORRELATIVES/SPECIAL STUDIES

Specimens will be collected for banking and archival purposes. Submission of samples for correlative studies is expected of all subjects at baseline and optional tumor biopsy will be performed for those who consent to it.

10.1 Sample Collection Guidelines

Prior to study enrollment, patients must have documented CDK12 loss on a prior biopsy (or cell-free DNA or other is allowed) of primary or metastatic tissue. Metastatic tissue is strongly preferred.

Willingness to provide archival tissue submission is mandatory. If archival tissue, contains inadequate tissue for NGS (i.e., less than 30% tumor content) or patient does not consent to fresh tissue biopsy, or fresh biopsy is not feasible, then patient may enroll in study if all other eligibility criteria are met. In general, visceral metastases are prioritized over soft tissue or lymph node, and least preferable are bone metastases.

Refer to Section 6.0 for tumor tissue and blood collection time points and Lab Manual for collection and processing details.

10.2 Specimen Banking

Patient samples (tissue and blood) collected for this study will be retained at the University of Michigan. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and

Disposition within all UMMS Research Repositories
https://research.medicine.umich.edu/office-research/biorepository/governance-policies.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This is a multi-center, prospective, one arm, 3 cohort study to evaluate the efficacy of immunotherapy in patients with metastatic cancers and CDK12 loss. Patients with metastatic castration resistant prostate cancer (mCRPC) will be enrolled in Cohort A until 25 evaluable patients are identified. Once Cohort A is full, mCRPC patients will enroll in Cohort C. Patients with other metastatic subtypes will be enrolled in Cohort B.

An Mini-Max Simon Two-Stage design will be used to assess ORR defined as a 50% decline in PSA from baseline in CDK12 loss of function metastatic CRPC patients. It is assumed that an ORR of 30% or more would be interesting for further study compared to a reference ORR of 10% based on the KEYNOTE-199 trial [35]. Accrual of 25 objective PSA response evaluable patients will provide 80% power to detect this difference in ORR with a type I error of 5%. Interim analysis will be completed after 15 objective PSA response evaluable patients (Cohort A only). If 2 or more patients have a PSA response, then the 2nd stage will open and accrue 10 more patients. If 6 or more patients out of 25 have a PSA response, then the treatment will be recommended for further study in this population.

Cohort B will accrue 15 patients with non-prostate histology. A reference ORR of 5% is assumed in patients with non-prostate histology. With 15 patients, we have 76% power to detect an ORR of 25% with a one-sided type I error of 5%. If 3 or more responses are seen in cohort B then we will conclude that there is preliminary evidence of activity.

Cohort C will accrue 25 mCRPC patients. A reference ORR of 10% is assumed, allowing 80% power to detect an ORR of 30% or more with a one-sided type I error of 5%. If 6 or more patients out of 25 have a PSA response, then the treatment will be recommended for further study in this population.

11.2 Sample Size and Accrual

The trial is expected to accrue the total study population of 65 patients harboring CDK12 loss, including 50 objective PSA response evaluable metastatic prostate cancer patients and 15 objective response evaluable patients with non-prostate tumor histology over 2 years.

11.3 Data Analyses Plans

Primary Endpoint Analysis:
The primary endpoint for Cohort A and Cohort C is overall response rate using PSA criteria. The primary analysis will include the response count and proportion with the associated exact 95% binomial confidence interval in the mCRPC cohort. If stage 2 is initiated, then the efficacy analysis methods for the reported response confidence interval will be as described by Koyama and Chen [33].

Secondary Endpoint Analysis:
Efficacy in Cohort B will be described using overall response rate (CR/PR) using RECIST 1.1 criteria. The response count and proportion will be reported with the associated 95% exact binomial confidence interval.

Safety and tolerability of, nivolumab and ipilimumab combination therapy followed by nivolumab monotherapy, or nivolumab monotherapy only, will be described by the frequency and severity of adverse events by CTCAE criteria. The proportion of patients removed from treatment due to AEs will be reported. The number and proportion of patients with dose reductions and/or holds will be reported separately and overall. Each measure will be reported for the entire trial and separately by cohort.

Secondary efficacy time-to-event endpoints including radiographic progression-free survival (rPFS), progression-free survival (PFS), duration of response (DOR) among responders, duration of therapy (DOT), time to progression (TTP) and overall survival (OS) will be reported using Kaplan-Meier methods. The median, if reached, and the 52-week event-free proportion with the associated 95% greenwood formula confidence interval will be reported for each endpoint. For subjects with metastatic CRPC, PSA progression-free survival and time to PSA progression by PCWG3 criteria will also be described for Cohort A using the same the Kaplan-Meier measures described previously. Objective tumor response in patients with measurable disease by RECIST 1.1 criteria will reported separately by location using PCWG3 recommendations and will include waterfall plots and counts with proportions and the associated 95% confidence intervals. Each endpoint will be reported for all patients if applicable and separately for each cohort.

Quality of Life (QoL) in subjects treated on protocol therapy will be described using EORTC-QLQ-C30 and BPI-SF measures. Baseline will be described using means or medians with an associated variance statistic. Change from baseline will be reported at each time point thereafter with similar descriptive statistics. Each measure will be reported for the overall population and separately by cohort. Each QoL change from baseline will be analyzed using a general linear model with repeated measures for an association with response.

Exploratory Endpoint Analysis

Tumor genome profiling by integrated DNA and RNA sequencing at baseline and optionally at progression will be described using figures representing the profiled patients. These figures will order patients by degree of response (PSA response for Cohort A and Cohort C; and RECIST response for Cohort B). A logistic model with response as the outcome may be used with specific markers as independent covariates to estimate an effect size if a profound pattern is seen. Differences seen in paired samples (baseline and progression) will be described individually and labeled as a responder/non-responder. Immune infiltration in tumor biopsies will be described using figures. Associations of the profiles with the response will be described using counts and proportions.

12.0 DATA AND SAFETY MONITORING

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor-Investigator (S-I)/Study Principal Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites

The Sponsor-Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined quarterly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a quarterly basis for independent review.

13.0 DATA MANAGEMENT

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- After subject enrollment
  - Subject Status
  - Demographics
- During study participation
  - All data should be entered online within 10 business days of data acquisition. Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

14.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

15.0 CLINICAL TRIAL MONITORING

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo a site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his/her study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate Coordinating Center personnel until they have been answered and resolved.

Monitoring of this study can include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes the first treatment cycle. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

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17.0 APPENDICES

APPENDIX A

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

APPENDIX B
Brief Pain Inventory (Short Form)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date:____/____/____ Time:_____

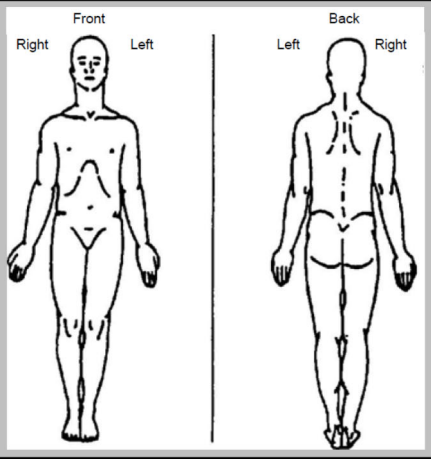
Name:_____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ___/___/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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APPENDIX C

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent