NCI Protocol #: N/A

DF/HCC Protocol #: 19-384
BMS Protocol #: CA209-8Y7
PCCTC Protocol #: c19-232

TITLE: A Phase 2 Multicohort Study of Nivolumab in Combination with Docetaxel and Androgen Deprivation Therapy in Metastatic Hormone Sensitive Prostate Cancer Patients with DNA Damage Repair Defects or Inflamed Tumors

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Agents
Nivolumab (Supplied by Bristol-Myers Squibb)
Docetaxel (Commercial)
Abiraterone acetate (Commercial)

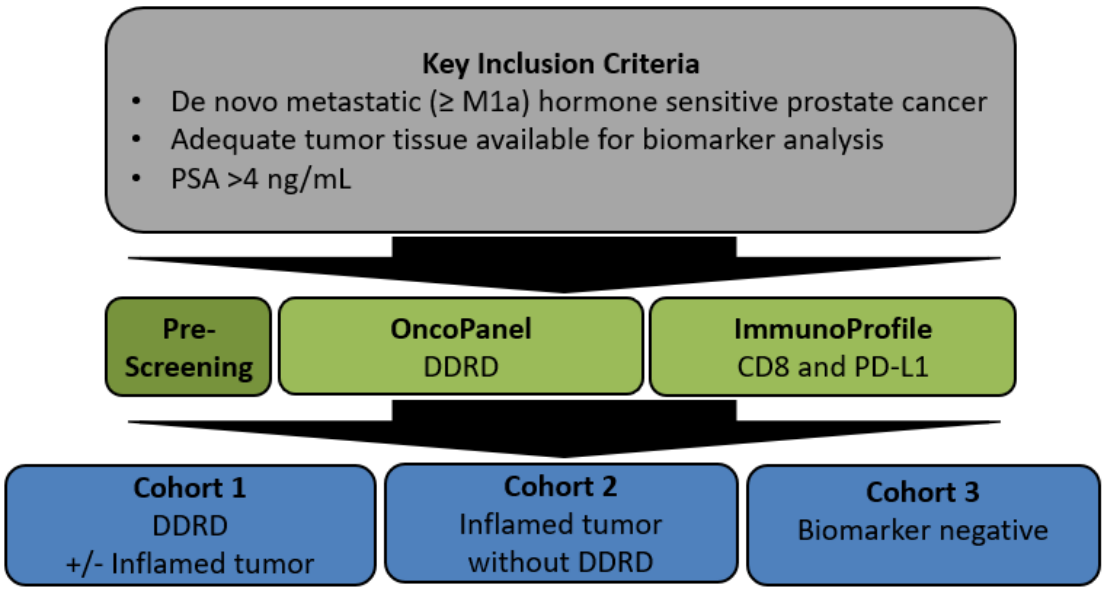
LHRH analogue (Commercial)

IND #: 143536
IND Sponsor: Xiao Wei, MD, MAS

Protocol Type / Version # / Version Date: Version 8.0 / February 21, 2024

SCHEMA

Cohort Allocation:



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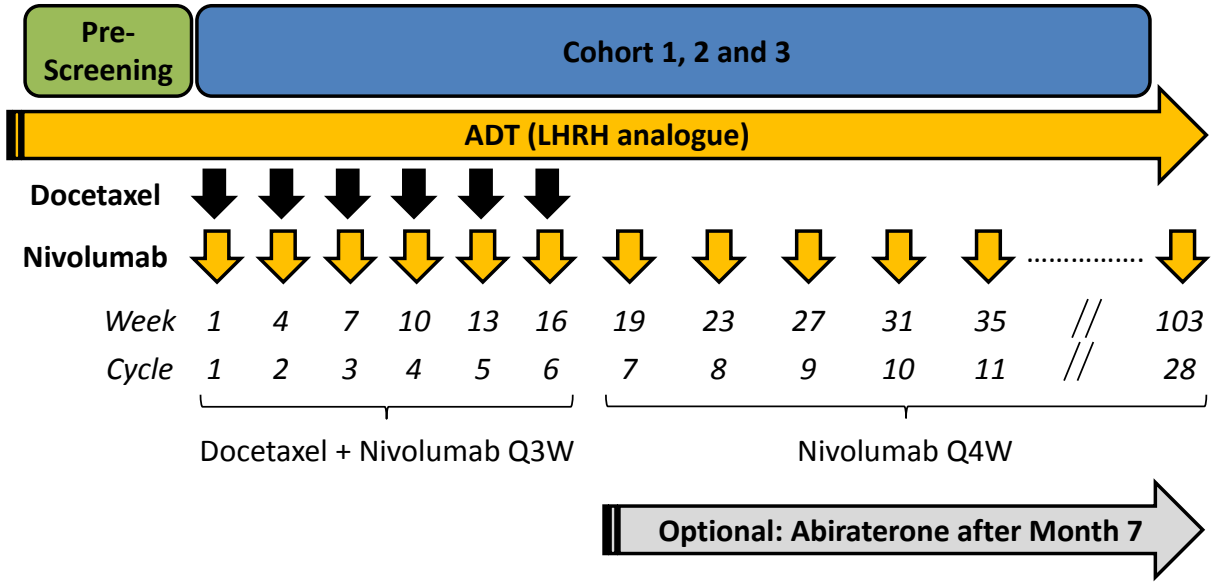

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ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
AR	Androgen receptor
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
CD279	Cluster of differentiation 279
cHL	Classical Hodgkin Lymphoma
Cavg	Average serum concentration
CI	Confidence interval
CIO	Center for Immuno-Oncology
CL	Clearance
CL_{ss}	Steady state clearance
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum serum concentration
Cmin	Minimum serum concentration
CNV	Copy number variation
CrCl	Creatinine Clearance
CRF	Case report form
CT	Computed Tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
CTMS	Clinical Trials Management System
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DDRD	DNA damage repair defects
DF/HCC	Dana-Farber/Harvard Cancer Center
DF/PCC	Dana-Farber/Partners CancerCare
dL	Deciliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ePPND	Enhanced pre- and postnatal development
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
GFR	Glomerular filtration rate
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FOXP3	Forkhead box P3
HBsAg	HBV surface antigen

HBV	Hepatitis B virus
HCV	Hepatitis C virus
hr	Hour
HuMAb	Human monoclonal antibody
IFN-γ	Interferon-gamma
IND	Investigational New Drug
IgG4	Immunoglobulin G4
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional Review board
IV	Intravenous
kg	Kilogram
LDH	Lactase dehydrogenase
LFT	Liver function test
LHRH	Luteinizing hormone-releasing hormone
LLN	Lower limit of normal
LN	Lymph node
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
mcl	Microliter
mCRPC	Metastatic castration resistant prostate cancer
MCV	Mean corpuscular volume
mg	Milligram
mHSPC	Metastatic hormone sensitive prostate cancer
min	Minute
mL	Milliliter
MLR	Mixed lymphocyte reaction
MMR-d	Mismatch repair deficient
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability – high
MTD	Maximum tolerated dose
N/A	Not applicable
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ODQ	Office of Data Quality
OHRS	Office for Human Research Studies
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCCTC	Prostate Cancer Clinical Trials Consortium
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand 2
PFS	Progression-free survival
PI	Principal investigator

PPK	Population pharmacokinetic(s)
PK	Pharmacokinetics
PSA	Prostate specific androgen
PT	Prothrombin Time
PTT	Partial thromboplastin time
PVC	Polyvinyl chloride
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q12W	Every 12 weeks
RBC	Red blood cell
RCC	Renal cell carcinoma
RNA-seq	RNA sequencing
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SCCHN	Squamous cell carcinoma of the head and neck
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SJS	Stevens-Johnson syndrome
$t_{1/2}$	Half-life
TCR	T cell receptor
TEN	Toxic epidermal necrolysis
TMB	Tumor mutation burden
TNBC	Triple-negative breast cancer
TSH	Thyroid stimulating hormone
TURP	Transurethral resection of the prostate
UC	Urothelial carcinoma
ULN	Upper limit of normal
US	United States
USPI	United State Product Insert
V_{ss}	Volume of distribution at steady state
WBC	White blood cell
WES	Whole exome sequencing
wnl	Within normal limits

1. OBJECTIVES

1.1 Study Design

This is an open-label, multicohort, phase 2 study of nivolumab in combination with docetaxel and androgen deprivation therapy (ADT) in patients with newly diagnosed (de novo) metastatic hormone sensitive prostate cancer (mHSPC). Patients whose tumor harbors DNA repair defect(s) (DDRD) or an inflamed tumor microenvironment by CD8 or PD-L1 staining will be prospectively enriched using the OncoPanel and ImmunoProfile assays, respectively. Three biomarker cohorts will be enrolled: Cohort 1 includes patients with DDRD with or without inflamed tumors, Cohort 2 includes patients with inflamed tumors without DDRD, and Cohort 3 includes patients with biomarker negative tumors. All patients will receive continuous ADT (luteinizing hormone-releasing hormone (LHRH) analogue), docetaxel 75 mg/m^2 plus nivolumab 360 mg intravenously (IV) every 3 weeks (Q3W) for 6 cycles, followed by nivolumab 480 mg IV every 4 weeks (Q4W) for up to 2 years in total duration. The primary endpoint is proportion of patients with PSA ≤ 0.2 ng/mL at 7 months from start of chemoimmunotherapy. Patients have the option of starting standard of care (SOC) abiraterone acetate with prednisone at the discretion of the treating physician after completing planned docetaxel chemotherapy and the 7-month primary endpoint is reached.

1.2 Primary Objectives

- To determine the proportion of subjects with PSA less than or equal to 0.2 ng/mL at 7 months from start of chemoimmunotherapy in each cohort

1.3 Secondary Objectives

- To determine the proportion of subjects with PSA less than or equal to 0.2 ng/mL before initiation of subsequent systemic therapy
- To estimate overall survival (OS)
- To estimate time to castration resistance
- To estimate time to clinical progression
- To estimate time to prostate specific antigen (PSA) or serologic progression
- To determine the objective response rate in subjects with measurable disease
- To assess safety and tolerability to chemohormonal-immunotherapy in the upfront management of mHSPC

1.4 Exploratory Objectives

- To assess changes in circulating Peripheral Blood Mononuclear Cells (PBMCs) subsets, chemokines and cytokines with treatment
- To quantify changes in circulating tumor cells (CTCs) and cell-free DNA (cfDNA) with treatment
- To characterize clinical outcomes in subgroups defined by the individual and joint utility of PD-L1 staining, CD8 staining, DDR status, tumor mutation burden (TMB), genomic alterations, and transcriptomic signatures

- To assess the immune microenvironment associated with different types of DDRD, and clinical outcomes by different types of DDRD (Cohort 1)
- To examine functional biomarkers of DDRD and their correlation with immune microenvironment and clinical outcomes (Cohort 1)
- To compare genomic and transcriptomic profiles of paired primary and metastatic biopsy tissues
- To correlate baseline genomic aberrations and immune infiltration with clinical outcomes in de novo mHSPC (screened patients)

2. BACKGROUND

2.1 Metastatic Hormone Sensitive Prostate Cancer

Prostate cancer affects approximately 165,000 men and results in approximately 30,000 deaths each year. PSA testing has allowed early detection of prostate cancer, and men diagnosed with localized disease have excellent prognosis (5-year OS near 100%). However, the incidence of distant metastasis has increased after 2010, related to a decline in PSA test utilization (Negoita 2018). At initial diagnosis, approximately 78% of prostate cancer are localized, 12% has spread to regional lymph nodes, and 5% have distant metastatic disease.

Primary ADT—with hormone ablation either by an LHRH analogue or orchiectomy with or without an antiandrogen—had been the mainstay of therapy for men diagnosed with mHSPC. OS and prognosis are related to the extent of disease as well as presentation (de novo vs. metachronous) (Sweeney 2021). When treated with ADT alone, patients with high volume metastatic disease have a poor prognosis with a median time to PSA progression of approximately 11 months and median time to clinical progression of approximately 14 months (Eisenberger 1998).

In recent years, the treatment paradigm for mHSPC has evolved. Three landmark phase 3 trials demonstrated that upfront intensification of treatment—by adding docetaxel chemotherapy or abiraterone acetate to ADT—significantly improves clinical outcomes in patients with mHSPC, including prolongation of OS (Sweeney 2015, James 2017, Fizazi 2017, Davis 2019, Armstrong 2019, Chi 2019). More recently, upfront triple therapy with ADT, docetaxel plus abiraterone acetate and ADT, docetaxel plus enzalutamide were shown to significantly improve radiographic PFS (rPFS) and OS compared to ADT plus docetaxel in patients with de novo mHSPC (Fizazi 2022, Smith 2022). Despite these advances, most patients eventually develop castration resistant or hormone resistant disease, the lethal form of prostate cancer.

This trial aims to evaluate whether the addition of PD-1 targeted immunotherapy (nivolumab) in combination with ADT plus docetaxel can delay time to development of castration-resistant prostate cancer (CRPC) and ultimately increase long-term outcomes in men with mHSPC.

2.2 IND Agent: Nivolumab

2.2.1 **Mechanism of action**

Nivolumab is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

2.2.2 **Summary of nonclinical studies**

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro. Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release.

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 μg•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.

2.2.3 **Summary of clinical studies**

The pharmacokinetics (PK), clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, clear-cell renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), urothelial carcinoma (UC), squamous cell carcinoma of the head and neck (SCCHN), in addition to other tumor types.

Nivolumab monotherapy is approved in multiple regions, including the United States (US) and European Union (EU), for unresectable or metastatic melanoma, previously treated metastatic NSCLC, previously treated advanced RCC, previously treated relapsed or refractory cHL, previously treated advanced or metastatic UC, and for the treatment of previously treated recurrent or metastatic SCCHN; it is also approved for previously treated CRC, previously

treated HCC, and the adjuvant treatment of melanoma in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for RCC in the US and unresectable melanoma in multiple countries, including the US and EU.

Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies for the treatment of several types of cancer. Single-dose nivolumab monotherapy was also investigated in a Phase 1b study of patients with sepsis who were also managed according to established best practice care for sepsis.

2.2.4 **Summaries clinical pharmacokinetics**

The PK of nivolumab was studied in subjects with cancer 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 (CL) decreases over time, with a mean maximal reduction from baseline values of approximately 25% resulting in a geometric mean (% coefficient of variation [CV%]) steady state clearance (CLss) of 8.2 mL/h (53.9%) in subjects with metastatic tumors. The decrease in CLss is not considered clinically relevant. The geometric mean (CV%) volume of distribution at steady state (Vss) is 6.8 L (27.3%), and 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 (Q2W), 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 Q2W. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, solid tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight (35 to 160 kg) had an effect on nivolumab CL, the effect was not clinically meaningful.

2.2.5 **Major route of elimination**

Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

2.2.6 **Safety profile**

Overall, the safety profile of nivolumab monotherapy in subjects with cancer is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. Most adverse events (AEs) were low-grade (Grade 1-2) with relatively few drug-related high-grade (Grade 3-4) AEs. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. For

nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies).

2.2.7 **Rational for proposed dose and regimen**

PPK and exposure response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens in subjects with cancer in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W is equivalent to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in subjects treated with nivolumab in clinical trials, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W. Using a PPK model, the overall distributions of nivolumab exposures (Cmax, Cavg, and Cmin after the first dose or at steady-state) are comparable between 3 mg/kg Q2W or 240 mg Q2W dosing regimens. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cavgss are predicted to be similar to those following nivolumab 3 mg/kg Q2W or 240 mg Q2W, while Cminss are predicted to be approximately 6% and 16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, maxss are predicted to be approximately ~3% and 43% higher, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures following 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens across body weights (35 to 160 kg) are predicted to be maintained well below corresponding exposures observed with the safe and well-tolerated 10 mg/kg nivolumab Q2W dosing regimen.

The FDA has approved the nivolumab 240 mg Q2W and 480 mg Q4W flat dose schedules. This study will use the nivolumab 360 mg Q3W schedule during the first 6 cycles, when nivolumab will be administered in combination with docetaxel chemotherapy. Subsequent nivolumab will be given at 480 mg Q4W.

2.3 Non-IND Agent 1: Docetaxel

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of cellular mitosis.

In prostate cancer cells, microtubule network has been shown to be critical for androgen receptor (AR) nuclear translocation and activity, and docetaxel decreases AR nuclear accumulation which likely contributes to the efficacy of docetaxel in prostate cancer (Zhu 2010).

Docetaxel is a commercially marketed product which has been approved by the FDA for multiple oncologic clinical indications. This includes advanced or metastatic breast cancer as single agent after chemotherapy failure, and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive breast cancer; non-small-cell lung carcinoma (NSCLC) as single agent for locally advanced or metastatic disease after platinum failure, and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC; untreated, advanced gastric adenocarcinoma with cisplatin and fluorouracil; locally advanced squamous cell carcinoma of

the head and neck (SCCHN) with cisplatin and fluorouracil for induction therapy; and metastatic castration resistant prostate cancer (mCRPC) as monotherapy given with prednisone (Refer to FDA approved package insert for additional information).

While docetaxel for the indication of mHSPC is not currently approved by the FDA, the OS benefit demonstrated in the phase 3 E3805 CHAARTED study has been considered practice changing, and ADT plus docetaxel is now considered a standard of care for patients with high-volume mHSPC deemed to be fit to receive chemotherapy (NCCN Guidelines v4.2018). The use of docetaxel in this protocol is exempt from the requirements of an IND as described under Title 21 CFS 312.2(b).

In this study, docetaxel will be administered at 75 mg/m^2 Q3W without prednisone for 6 cycles based on the E3805 CHAAARTED trial. This is considered a standard regimen and will be delivered per institutional standards.

2.4 Non-IND Agent 2: LHRH analogue

LHRH analogues, such as leuprolide, goserelin acetate, and degarelix, are long-acting analogues of the native LHRH peptide that result in suppression of testicular steroidogenesis. LHRH analogues are administered subcutaneously or intramuscularly (Refer to FDA approved package insert for additional information). LHRH analogues are FDA approved for the treatment of metastatic prostate cancer and will be administered per institutional standards in this study.

2.5 Non-IND Agent 3: Abiraterone acetate

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Abiraterone acetate is administered orally at a dose of 1,000mg daily in combination with prednisone 5mg daily or BID (Refer to FDA approved package insert for additional information). Abiraterone acetate is FDA approved for the treatment of metastatic hormone sensitive prostate cancer as well as metastatic hormone resistant prostate cancer.

In this study, patients have the option of starting SOC abiraterone acetate with prednisone at the discretion of the treating physician and per institutional standards after completing planned docetaxel chemotherapy and the 7-month primary endpoint is reached.

2.6 Study Rationale

2.6.1 Rationale for Target Patient Population

In recent years, there has been significant enthusiasm surrounding tumor immunotherapy, specifically with immune checkpoint antibodies targeting the immune inhibitory co-receptors PD1, PD-L1, and CTLA-4. However, these agents have failed to demonstrate significant single-agent activity in mCRPC. Two phase 3, randomized, placebo-controlled trials of ipilimumab in

the post-docetaxel and pre-docetaxel mCRPC settings failed to meet their primary endpoint of OS (Kwon 2014, Beer 2017). PD-1 inhibition alone in mCRPC leads to low objective response rates ranging from 0% to 10% (Topalin 2012, De Bono 2018). More recently, the addition of atezolizumab to enzalutamide failed to improve overall survival compared to enzalutamide alone in men with mCRPC (Powles 2022).

An opportunity exists to investigate the role of immunotherapy strategies in earlier disease states during prostate cancer progression. There is also a need to conduct trials that prospectively select patients best positioned to respond to immunotherapy strategies.

This study aims to investigate the activity of nivolumab in combination with docetaxel and ADT in men with newly diagnosed, treatment-naive mHSPC. Long-term follow-up from the phase 3 E3805 CHAARTED study showed that OS benefit was observed in mHSPC patients with high-volume disease (HR 0.72, p=0.0018). This study will enroll mHSPC patients with high volume of metastatic disease, prospectively enriching for those whose tumors harbor DNA repair defect(s) (OncoPanel) or an inflamed tumor microenvironment (ImmunoProfile). All patients will receive continuous ADT, 6 cycle of upfront docetaxel plus nivolumab, followed by continuation of nivolumab for up to 2 years in total duration. Patients have the option of starting SOC abiraterone acetate with prednisone at the discretion of the treating physician and per institutional standards after completing planned docetaxel chemotherapy and the 7-month primary endpoint is reached.

2.6.2 **Rationale for Chemohormonal-Immunotherapy in mHSPC**

ADT as well as cytotoxic chemotherapies have immunostimulatory effects, including induction of tumor antigen-directed cytolytic activity **(**Olson 2017, Kroemer 2013, Hodge 2014**)**. In the preclinical Myc-CaP prostate cancer mouse model, ADT was shown to induce a pro-inflammatory infiltrate during the early post-castration period, which subsequently diminishes with the development of castration resistance (Shen 2018). Immune checkpoint inhibition (with anti-CTLA-4 with or without anti-PD-1) significantly delayed the emergence of castration resistant disease and prolonged OS in these mice when administered in the peri-castration period, but not if treatment is delayed. Furthermore, immune checkpoint inhibition was ineffective when delivered without ADT, suggesting that ADT is required for immune-mediated activity in the peri-castration setting (Shen 2018).

Although cytotoxic chemotherapy has historically been considered immunosuppressive, it is now evident that certain chemotherapies can augment tumor immunity. In preclinical models, immunogenic chemotherapy promotes intratumoral T cell infiltration and expression of PD-1 and PD-L1 within the tumor microenvironment, thereby sensitizing tumors to immune checkpoint blockade (Pfirschke 2016). *In vitro*, docetaxel upregulates expression of tumor antigens in LNCaP (prostate cancer) and other cell lines and enhances CTL-mediated killing; this mechanism is distinct from immunogenic cell death (Hodge 2014).

The combination of PD-1/PD-L1 axis inhibition and cytotoxic chemotherapy is now shown to be safe and clinically active for patients with advanced malignancies. In August 2018, the FDA granted full approval to frontline pembrolizumab (anti-PD-1) in combination with standard

chemotherapy (pemetrexed plus cisplatin or carboplatin) for patients with metastatic NSCLC, based on improvement in OS and progression-free survival (PFS) compared to chemotherapy alone in the phase 3 KEYNOTE-189 trial (Gandhi 2018). The frontline combination of atezolizumab (anti-PD-L1) with chemotherapy (carboplatin plus etoposide) significantly improves OS and PFS compared to chemotherapy alone in patients with extensive-stage small cell lung cancer (ES-SCLC) in the phase 3 Impower133 trial (Horn 2018). Early phase studies reported that the combination of pembrolizumab and docetaxel or gemcitabine is safe and clinically active in advanced or metastatic urothelial carcinoma after platinum-based chemotherapy (Parikh 2018). A multi-arm study of nivolumab combined with various standard chemotherapy in advanced NSCLC, which included docetaxel chemotherapy in arm D, showed that the combination of nivolumab and chemotherapy is well tolerated (Kanda 2016). Consistent with this, a separate feasibility study reported that the combination of nivolumab and docetaxel is safe in NSCLC after platinum-based chemotherapy (Shimokawa 2017). Most recently, the combination of atezolizumab and nab-paclitaxel was shown to prolong PFS in patients with metastatic triple-negative breast cancer (TNBC) compared to nab-paclitaxel alone in a phase 3 randomized placebo-controlled trial (Impassion 130, Schmid 2018).

These studies suggest that the combination PD-1 inhibition with ADT and docetaxel chemotherapy may be a viable strategy with synergistic activity as initial treatment in mHSPC. No studies to date have prospectively investigated this combination strategy in the upfront management of mHSPC.

2.6.3 **Rationale for Prospective Biomarker-Based Patient Selection**

DNA repair defects drive genomic instability—a hallmark of cancer—which promotes tumor immunogenicity (Mouw 2017). Whole exome sequencing of advanced prostate cancer indicates that the prevalence of mismatch repair (MMR) deficiency and microsatellite instability (MSI) ranges between 2% and 12% (Pritchard 2014, Robinson 2015). Furthermore, other genomic alterations in the DNA repair pathway, including in *BRCA2*, *BRCA1* and *ATM*, are reported to occur in approximately 19% of patients with advanced prostate cancer (Robinson 2015). The most compelling evidence that DDRD represents an important biomarker of immunotherapy response is the disease-agnostic activity of pembrolizumab in patients with MSI-high (MSI-H) or MMR deficient (MMR-d) advanced solid malignancies (Le 2015). More recently, emerging data suggest that other DNA repair defects including *BRCA1*, *BRCA2*, *ATM*, and *CDK12* may also predict increased response to immune checkpoint blockade in patients with mCRPC **(**De Bono 2018, Boudadi 2018, Wu YM 2018).

Various biomarker studies in the context of anti-PD-1/PD-L1 trials have also supported the hypothesis that PD-1/PD-L1 inhibition is most effective in patients with pre-existing antitumor immunity, reflected by an “inflamed” tumor microenvironment. Characteristics of this inflamed phenotype include dense CD8+ T cell infiltration, PD-L1 expression (in tumor and/or immune cells), and expression of T-effector gene signatures (Tumeh 2014, Ribas 2015, McDermott 2018). PD-L1 has been shown to be expressed in moderate to high levels in approximately 50% of primary prostate cancer, and this expression is an independent indicator for biochemical recurrence (Gevensleben 2015). While a major proportion of patients with prostate cancer lack evidence of spontaneous T cell infiltration within their tumors at baseline, a small subset of

patients harbor T cell inflamed tumors (Spranger 2016). Furthermore, combination strategies with immunostimulatory effects may restore T cell trafficking into non-T cell inflamed tumors.

This study aims to prospectively enrich for mHSPC patients best positioned to respond to nivolumab combined with docetaxel and ADT, by selecting for those whose tumors harbor DDRD (OncoPanel, Cohort 1) or an inflamed tumor microenvironment (ImmunoProfile, Cohort 2). Because the optimal biomarker that predicts clinical benefit is unknown, a third cohort of biomarker negative patients will also be enrolled (Cohort 3).

2.6.4 **Rationale for Primary Objective**

PSA nadir ≤0.2 ng/mL at 7 months from ADT initiation was shown to be prognostic for OS in mHSPC patients treated with ADT alone or ADT plus upfront docetaxel in the phase 3 E3805 CHAARTED trial (Harshman 2018). Approximately 45% of patients treated with ADT plus docetaxel achieved PSA ≤0.2 ng/mL at 7 months (Harshman 2018). Among 397 patients treated with ADT plus docetaxel in CHAARTED, 214 (54%) patients had high-volume disease and no prior local therapy (de novo presentation). Of these 214 patients, 28% achieved PSA ≤0.2 ng/mL at 7 months (unpublished data from E3805 investigators).

This study hypothesizes that multiagent chemohormonal-immunotherapy with ADT, docetaxel and nivolumab will improve long-term outcomes in mHSPC patients, with a higher proportion of patients achieving PSA ≤0.2 at 7 months. Furthermore, the activity of this combination strategy may be most active in patients whose tumors harbor DDRD or a pre-existing inflamed tumor microenvironment.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

3.1.1 Newly diagnosed histologically confirmed prostate adenocarcinoma within 6 months prior to study registration with evidence of distant metastasis on conventional imaging
- Distant metastasis is defined by non-regional lymph node(s) metastasis (M1a), bone metastasis (M1b), and/or other site(s) of metastatic disease (M1c).
- Conventional imaging consists of CT, MRI or radionuclide bone scan

3.1.2 Subjects must be candidate for docetaxel chemotherapy per Investigator's judgement.

3.1.3 Age ≥18 years

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)
- Subjects with ECOG performance status of 2 are only eligible if the performance status decline is attributed to metastatic prostate cancer

3.1.5 Serum PSA > 4.0 ng/mL before initiation of ADT

3.1.6 Serum testosterone > 100 ng/dL before initiation of ADT

- Subjects whose testosterone level is unknown before initiation of ADT may be allowed after discussion with Sponsor-Investigator.

3.1.7 Grade ≤ 1 peripheral neuropathy, defined as asymptomatic or paresthesia and/or decreased deep tendon reflexes is allowed.

3.1.8 Subjects must have adequate organ and marrow function as defined below:

Absolute neutrophil count	≥1,500 /mcL
Platelets	≥100,000 /mcL
Total bilirubin	≤1.5 × institutional upper limit of normal • Exception: Subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology) may be allowed after consultation with treating physician
AST(SGOT) and ALT(SGPT)	≤2.5 × institutional upper limit of normal • Exception: ≤5 x institutional upper limit of normal in subjects with liver metastasis
Creatinine (Cr) and creatinine clearance (CrCl)	Cr <1.6 mg/dL or CrCl ≥30 mL/min; CrCl should be calculated using the Cockcroft-Gault formula: CrCl (mL/min) = $\frac{(140\text{-Age}) \times \text{Body weight (Kg)}}{72 \times \text{Serum creatinine (mg/dL)}}$
PT, INR and PTT	≤ 1.5 x institutional upper limit of normal • Exception: Subjects who are on a stable regimen of therapeutic anticoagulation for an appropriate clinical indication may be enrolled

3.1.9 Availability of adequate baseline tumor tissue for integral biomarker analysis and correlative studies:

- Sources of tumor tissue allowed are (1) prostate biopsy, (2) transurethral resection of the prostate tissue (TURP), (3) trans urethral resection of bladder tumor tissue (TURBT) with contiguous spread of prostate cancer to the bladder, and (4) metastatic biopsy tissue excluding bone and lymph node metastases (e.g. lung or liver biopsies are acceptable).
- For OncoPanel, submit at least one (1) H&E slide and ten (10) 5-micron thick serially sectioned unstained formalin-fixed paraffin-embedded (FFPE) slides. Biopsy should contain at least 20% tumor involvement with the highest Gleason score(s). If requested tissue is unavailable, a lower number of 4-micron or 5-micron slides and/or slides containing lower tumor involvement may be accepted after discussion with the Sponsor-Investigator.
- For ImmunoProfile, submit at least one (1) H&E slide and one (1) 5-micron thick serially sectioned unstained, freshly cut, FFPE slide. Biopsy should contain at least 50% tumor involvement with the highest Gleason score(s). If requested tissue is unavailable, a 5-micron slide containing lower tumor involvement may be accepted after discussion with the study Sponsor-Investigator.

- Submission of one (1) H&E slide and at least one (1) FFPE tissue core block with at least 3mm^2 tumor area with the highest Gleason score is an acceptable alternative to unstained FFPE slides.
- Subjects who have insufficient baseline prostate biopsy tissue for OncoPanel analysis but have baseline metastatic biopsy tissue available may have OncoPanel analysis performed using metastatic biopsy tissue. Successful OncoPanel testing (but not ImmunoProfile) of metastatic biopsy tissue is acceptable from any source including lymph node or bone, after discussion with the study Sponsor-Investigator.
- For Exploratory Correlative Studies, at least 1 tissue core block (preferred) or one (1) H&E slide and twelve (12) 5-micron thick FFPE slides with unstained, freshly cut, serial sections from biopsy cores containing at least 20% tumor involvement with the highest Gleason score(s) will be requested, if available.
- Tissue should be submitted with redacted pathology report.

3.1.10 Successful OncoPanel and ImmunoProfile biomarker analysis for allocation into a study cohort during pre-screening

- Subjects whose tumors harbor somatic or germline homozygous deletions and/or deleterious mutations in a DDR gene using OncoPanel will be assigned to Cohort 1, regardless of ImmunoProfile results
    - DDR genes include and are not limited to *BRCA2*, *ATM*, *CHEK2*, *BRCA1*, *PALB2*, *RAD51D*, *ATR*, *NBN*, *PMS2*, *GEN1*, *MLH1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, *FAM175A*, and *CDK12*
    - Deleterious mutations are defined as loss of function, splice site, nonsense, or frameshift mutations, and determination will be made between DFCI molecular pathology and study Sponsor-Investigator
    - Tumors identified as mismatch repair deficient (MMR-d) or microsatellite instability high (MSI-H) will also be included in Cohort 1
    - Patients with germline DDRD or MMR-d/MSI-H (Lynch Syndrome) or tumors with DDRD or MMR-d/MSI-H identified in another CLIA-certified laboratory (e.g., Foundation Medicine) using prostate or metastatic tissue may be assigned to Cohort 1 after discussion with the Sponsor-Investigator. If archival tissue is available, it will be requested for OncoPanel testing; however, results will not influence eligibility.
    - Subjects who are eligible for Cohort 1 may proceed to main study screening and start study treatment while ImmunoProfile results are pending.
- Subjects whose tumors are PD-L1 positive and/or CD8+ T cell inflamed using ImmunoProfile without the presence of DDRD will be assigned to Cohort 2
    - PD-L1 positivity will be defined as Combined Positive Score (CPS) ≥ 1, which is the number of PD-L1 staining cells (e.g., tumor cells, immune cells) divided by the total number of tumor cells, multiplied by 100
    - CD8+ T cell inflammation will be defined as CD8+ T cell density ≥ 200, which is the number of CD8+ cells divided by the surface area of a region of interest (mm^2)

- Subjects whose tumors do not harbor DDRD and are PD-L1 negative with low CD8+ T cell infiltration will be assigned to Cohort 3
- Subjects whose prescreening is unsuccessful for cohort allocation or whose biomarker status matches that of a filled cohort will not be eligible
    - Subjects who underwent successful ImmunoProfile pre-screening but failed OncoPanel pre-screening may be allocated to Cohort 2 or Cohort 3 based on ImmunoProfile results and assuming DDRD negativity, at the discretion of the Sponsor-Investigator.
- Before one of the study cohorts enrolls 15 of 20 subjects (Cohort 3 is anticipated to complete accrual first), subjects may undergo main study screening when ImmunoProfile and OncoPanel analyses are ongoing, and may proceed to study treatment if they meet all eligibility criteria with the exception that OncoPanel analysis is ongoing. These patients will be allocated into their respective cohort after OncoPanel results return.

3.1.11 Willingness to provide leftover metastatic biopsy tissue for correlative studies, if obtained for clinical purposes

3.1.12 Based on its mechanism of action and data from animal studies, nivolumab can cause fetal harm. For this reason non-sterilized men who are sexually active with a female partner of childbearing potential treated or enrolled on this protocol must agree to use adequate contraception prior to the study, for the duration of study participation, and for 5 months after last dose of nivolumab administration

- Adequate contraception includes male condom plus spermicide
- Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception
- Subjects in this study should refrain from sperm donation

3.1.13 Ability to understand and the willingness to sign a written informed consent document, or have a legally authorized representative sign on the subject's behalf

3.2 Exclusion Criteria

3.2.1 Subjects must not have received prior ADT (LHRH analogue ± antiandrogen), chemotherapy, or immunotherapy for prostate cancer. The following exception is allowed:

- Subjects who have initiated ADT prior to study registration and are able to complete biomarker pre-screening, cohort allocation, and start C1D1 study chemoimmunotherapy ≤140 days from initiation of ADT are allowed
    - The 140 day window commences at the start of either the antiandrogen agent or LHRH analogue, whichever is earlier
- Antiandrogens (e.g., bicalutamide or flutamide) may be used in addition to LHRH analogue ≤60 days before initiation of LHRH analogue to cover the testosterone

surge associated with certain LHRH agonists but must be discontinued prior to study registration
- Second-generation hormonal agents (e.g., abiraterone acetate) are not allowed

3.2.2 Subjects must not have undergone prostatectomy
- Prostate radiation is allowed before or after study enrollment and may be delivered concurrently with study chemoimmunotherapy, per provider discretion, assuming adequate prostate biopsy tissue is collected before prostatic radiation
- Metastasis-directed radiation is allowed before or after study enrollment and may be delivered concurrently with study chemoimmunotherapy, per provider discretion

3.2.3 Subjects must not have PSA increase greater than 50% from its nadir (lowest value) since starting ADT to the time of study registration

3.2.4 Subjects who are receiving any other investigational agents

3.2.5 Any previous treatment with a PD-1 or PD-L1 inhibitor

3.2.6 Subjects with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other AEs

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to docetaxel (including any drugs formulated with polysorbate 80), nivolumab, or LHRH analogue (e.g., leuprolide, goserelin acetate, degarelix)

3.2.8 History of another primary malignancy, except for:
- Malignancy treated with curative intent and with no known active disease for ≥2 years before the first dose of study treatment and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

3.2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.10 Major surgical procedure as defined by the Site Investigator within 28 days prior to the first dose of chemoimmunotherapy

3.2.11 Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome. HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for nivolumab to be less clinically active in this population. In addition, these subjects are at increased risk of lethal infections when treated with marrow-suppressive chemotherapy

3.2.12 History of allogeneic bone marrow or organ transplantation

3.2.13 Active or prior documented autoimmune or inflammatory disorders, including inflammatory bowel disease (e.g., Crohn's disease), systemic lupus erythematosus, Sarcoidosis syndrome, Grave's disease, rheumatoid arthritis, hypophysitis, uveitis, with the following exceptions:

- Vitiligo or alopecia
- Hypothyroidism stable on hormone replacement
- Chronic skin condition that does not require systemic therapy
- Celiac disease controlled by diet alone
- Subjects with inactive disease in the last 5 years may be included but only after consultation with the study physician
- Type 1 diabetes mellitus on insulin therapy

3.2.14 Active infection including tuberculosis, hepatitis B (known positive HBV surface antigen [HBsAg]), or hepatitis C (HCV)

- Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible
- Subjects with positive HCV antibody are eligible if polymerase chain reaction is negative for HCV RNA

3.2.15 Concurrent or prior use of immunosuppressive medication within 14 days before the first dose of study chemoimmunotherapy, with the following exceptions:

- Premedication for docetaxel with oral dexamethasone or other corticosteroid (See Section 5.1)
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intraarticular injection)
- Systemic corticosteroids at physiologic doses not exceeding 10mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., premedication for iodinated contrast allergy before CT scan)

3.3 Inclusion of Minorities

Men of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

Confirmation of eligibility will be completed centrally by the Prostate Cancer Clinical Trials Consortium (PCCTC) prior to treatment start. A record of patients who fail to meet eligibility

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

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible subjects in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any subject not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

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

4.2 Registration Process for DF/HCC Institutions

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

4.3 General Guidelines for Other Investigative Sites

Eligible subjects will be entered on study centrally at the Dana-Farber Cancer Institute via the PCCTC. All sites should contact the PCCTC Project Manager to verify cohort slot availabilities.

Following registration, subjects should begin protocol therapy within 30 business days. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If the subject does not receive protocol therapy following registration, the subject must be taken off-study, which will be updated in the CTMS (OnCore) with an appropriate date and reason entered via regular data reports provided to DF/HCC by the PCCTC.

4.4 Registration Process for Other Investigative Sites

To register a subject, the registration packet should be completed by the participating site and e-mailed to the PCCTC Project Manager. Please see appendix B for registration requirements.

The PCCTC Project Manager will email the participating site to verify eligibility. The PCCTC will notify the DF/HCC Project Manager, who will follow DF/HCC policy (REGIST-101) and register the subject on the protocol in OnCore. The PCCTC Project Manager will e-mail the subject study number to the participating site.

5. TREATMENT PLAN

5.1 Treatment Regimen

After biomarker prescreening (See Section 9), eligible subjects will be enrolled into their respective treatment cohort (Cohort 1: DDRD +/- Inflamed tumor; Cohort 2: Inflamed tumor without DDRD; Cohort 3: Biomarker negative). Cohort 3 is anticipated to complete accrual first, and Cohort 1 is anticipated complete accrual last. Subjects whose prescreening is unsuccessful for cohort allocation or whose biomarker status matches that of a filled cohort will not be eligible, with the following exceptions.

1) Before one of the study cohorts enrolls 15 of 20 patients (Cohort 3 is anticipated to complete accrual first), subjects may undergo main study screening when ImmunoProfile and OncoPanel analyses are ongoing, and may proceed to C1D1 treatment if they meet all eligibility criteria with the exception that OncoPanel analysis is ongoing. These patients will be allocated into their respective cohort after OncoPanel results return.

2) Subjects who underwent successful ImmunoProfile pre-screening but failed OncoPanel pre-screening may be allocated to Cohort 2 or Cohort 3 based on ImmunoProfile results and assuming DDRD negativity, at the discretion of the Sponsor-Investigator.

All enrolled subjects will receive continuous ADT (LHRH analogue), docetaxel 75 mg/m^2 plus nivolumab 360 mg IV Q3W for 6 cycles, followed by nivolumab 480 mg IV Q4W for up to 2 years in total duration.

LHRH analogue will be administered per manufacturer's instructions and institutional standards and may be initiated prior to study registration if ≤ 140 days have elapsed between initiation of ADT and C1D1 study chemoimmunotherapy (See Section 3.1). Examples of LHRH regimens include leuprolide (Lupron Depot) 22.5 mg IM Q12W, goserelin acetate (Zoladex) 3.6 mg SC Q4W, and degarelix (Firmagon) 240 mg SC starting dose followed by degarelix 80 mg SC Q4W.

The first 6 cycles of docetaxel and nivolumab will be administered concurrently every 3 weeks, with 21 consecutive days defined as a treatment cycle. C1D1 of nivolumab plus docetaxel must commence within 140 days of ADT initiation (See Section 3.1).

Three-weeks after completing 6 cycles of chemoimmunotherapy, nivolumab will be administered every 4 weeks with 28 consecutive days defined as a treatment cycle, for up to 22 additional cycles (2 years in total duration of nivolumab).

All treatment will be administered on an outpatient basis. LHRH analogue will be administered continuously without dose interruptions to maintain castrate-level serum testosterone levels for the full duration of the study. Docetaxel (up to 6 cycles) and nivolumab (up to 28 cycles) will be administered until disease progression (radiographic or clinical; see Section 11) or unacceptable toxicity.

Patients have the option of starting SOC abiraterone acetate 1000mg daily with prednisone 5mg daily or BID at the discretion of the treating physician and per institutional standards after completing planned docetaxel chemotherapy and the 7-month primary endpoint is reached.

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

Table 1. Regimen Description: Cycles 1-6

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
LHRH analogue (e.g., leuprolide, goserelin acetate, degarelix)*	No pre-medications	Per manufacturer's instructions and institutional standards (e.g., Lupron 22.5 mg IM Q12W, Zoladex 3.6 mg SC Q4W, Firmagon 240 mg SC starting dose followed by 80mg SC Q4W)			
Nivolumab	No pre-medications	360 mg	IV 30 min +/- 5 min	Day 1 Week 1	21 days (3 weeks)
Docetaxel	Premedicate with oral dexamethasone 8 mg BID on days -1, 0, and 1**	75 mg/m^2	IV 1 hr +/- 10 min after completion of nivolumab	Day 1 Week 1	21 days (3 weeks)
* May be started ≤140 days before Cycle 1 Day 1 Nivolumab + Docetaxel. **To prevent or reduce the severity of hypersensitivity reactions and fluid retention. Alternative schedules for dexamethasone or other corticosteroid premedications are allowed per institutional standards.					

Table 2. Regimen Description: Cycles 7-28

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
LHRH analogue (e.g., leuprolide, goserelin acetate, degarelix)*	No pre-medications	Per manufacturer's instructions and institutional standards (e.g., Lupron 22.5 mg IM Q12W, Zoladex 3.6 mg SC Q4W, Firmagon 240 mg SC starting dose followed by 80 mg SC Q4W)			
Nivolumab	No pre-medications	480 mg	IV 30 min +/- 5 min	Day 1 Week 1	28 days (4 weeks)
* May be started ≤140 days before Cycle 1 Day 1 Nivolumab + Docetaxel.					

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1 (Docetaxel + Nivolumab)

C1D1 results, obtained within 72 hours prior to treatment, must meet the following eligibility parameters to start treatment and be reviewed before treatment:

Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,000/mcL
Total bilirubin	≤1.5 × institutional upper limit of normal except for subjects with confirmed Gilbert's syndrome
AST(SGOT) and ALT(SGPT)	≤2.5 × institutional upper limit of normal or ≤5 x institutional upper limit of normal in subjects with liver metastasis
Creatinine or creatinine clearance	Cr <1.6 mg/dL or CrCl ≥30 mL/min (See Section 3.1.7)

5.3 Agent Administration

5.3.1 **Nivolumab**

Nivolumab will be administered intravenously (IV) on Day 1 of every 21-day cycle at a flat dose of 360 mg during Cycle 1 through Cycle 6, before administration of docetaxel. For subsequent cycles, nivolumab will be administered IV on Day 1 of every 28-day cycle at a flat dose of 480 mg without docetaxel. All visits have a window of ± 3 days (See Section 10 for Study Calendar).

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

Nivolumab injection is to be administered as an IV infusion over 30 minutes through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. Nivolumab should not be infused concomitantly in the same IV line with other medicinal products.

Nivolumab can cause severe infusion reactions, which have been reported in < 1.0% of subjects in clinical trials. Nivolumab should be discontinued in patients with severe or life-threatening infusion reactions. For subjects with mild or moderate infusion reactions, the rate of infusion should be interrupted or slowed (See Section 6).

No premedication or IV hydration are required for nivolumab. Subjects will be observed for 1 hour after completion of nivolumab infusion before administration of docetaxel for each cycle of docetaxel plus nivolumab coadministration.

5.3.2 **Docetaxel**

Docetaxel will be administered IV on Day 1 of every 21-day cycle at a dose of 75 mg/m^2 during Cycle 1 through Cycle 6, starting 1 hour ± 10 minutes after completion of nivolumab infusion

Premedication with dexamethasone 8 mg twice daily (BID) on days -1, 0, and 1 is required to prevent or reduce the severity of hypersensitivity reactions and fluid retention. Alternative schedules for dexamethasone or other corticosteroid premedication are allowed per institutional standards (See Section 5.1). Severe hypersensitivity reactions characterized by generalize rash or erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who receive a 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of docetaxel infusion and administration of appropriate therapy (See Section 6). Docetaxel must not be given to patients who have a history of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80.

Docetaxel preparation and administration, as well as premedication with antiemetics, will be according to manufacturer's instructions and institutional standards. No IV hydration is required for docetaxel.

5.3.3 **LHRH analogue**

LHRH analogue will be administered according to manufacturer's instructions and institutional standards. Examples include Lupron 22.5 mg IM Q12W, Zoladex 3.6 mg SC Q4W, and Firmagon 240 mg SC starting dose followed by 80 mg SC Q4W.

LHRH analogue will be administered continuously without dose interruptions to maintain castrate-level serum testosterone levels for the full duration of the study.

5.3.4 **Abiraterone Acetate**

Patients have the option of starting SOC abiraterone acetate 1000mg daily with prednisone 5mg daily or BID at the discretion of the treating physician and per institutional standards after completing planned docetaxel chemotherapy and the 7-month primary endpoint is reached. Patients who initiate abiraterone and prednisone will be required to have LFTs checked every two weeks for at least two months on abiraterone and prednisone.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 **Nivolumab**

No formal pharmacokinetic drug-drug interaction studies have been conducted with nivolumab, and there are no contraindications listed in the US labeling of nivolumab. Nivolumab should not be infused concomitantly in the same IV line with other medicinal products.

5.4.2 **Docetaxel**

In vitro drug interaction studies revealed that docetaxel is metabolized by the cytochrome P450 3A4 (CYP3A4) isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4. Because there is a potential for interaction of docetaxel with other concomitantly administered drugs through the CYP3A4 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving docetaxel, close monitoring for toxicity and docetaxel dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s). The Sponsor-Investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

After completion of docetaxel chemotherapy (Cycle 1-6), medications that are strong inducers/inhibitors or substrates of CYP3A may be restarted at least 1 week after the last docetaxel administration.

Premedication with dexamethasone 8 mg BID on days -1, 0, and 1 prior to infusion is required to prevent or reduce the severity of hypersensitivity reactions and fluid retention. Alternative schedules for dexamethasone or other corticosteroid premedications are allowed per institutional standards (See Section 5.1).

5.4.3 **LHRH analogue**

Subjects must not receive testosterone supplementation while on study therapy. Supportive care will be delivered per institutional standards.

5.4.4 **Abiraterone acetate**

Abiraterone acetate is a substrate of CYP3A4. In a dedicated drug trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Concomitant strong CYP3A4 inducers should be avoided during treatment with abiraterone acetate. If a strong CYP3A4 inducer must be co-administered, abiraterone acetate dose/frequency should be increased (Appendix C). In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug. In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate.

Supportive care will be delivered per institutional standards.

5.5 Criteria for Taking a Participant Off Protocol Therapy

LHRH analogue will be administered continuously without dose interruptions to maintain castrate-level serum testosterone levels for the full duration of the study.

Duration of docetaxel and nivolumab will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to AE(s), docetaxel may continue for 6 cycles and nivolumab may continue for 28 cycles or until one of the following criteria applies:

- Progressive disease: Development of documented clinical progression or radiologic progression by PCWG3 criteria with serum testosterone < 50 ng/dL (See Section 11)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Subject demonstrates an inability or unwillingness to comply with the study medication regimen and/or documentation requirements
- Withdrawal by subject: Subject decides to withdraw from the protocol therapy
- Dosing noncompliance
- Physician decision: General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the treating investigator

Study treatment will be continued for subjects who have increasing PSA without radiographic or clinical progression. Serial PSA measurements will be obtained; however, PSA increase alone is not considered a reliable measure of disease progression and should not be the only indication to discontinue treatment.

Subjects will be removed from the protocol therapy when any of the above criteria apply.

The reason for removal from protocol therapy, and the date the subject was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the subject.

When a subject is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment and/or Off-Study information will be updated in OnCore via regular data reports provided to DF/HCC by the PCCTC.

5.6 Duration of Follow Up

All subjects, including those who discontinue chemotherapy and/or immunotherapy early, will be followed until radiographic progression (PCWG3 criteria) assessed by treating physician, death, withdrawal of consent, or study termination, whichever occurs first. After radiographic progression, subjects will be followed for overall survival annually via chart review and/or telephone call until study termination. Subjects removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE (See Section 10, Study Calendar).

At the time of the pre-screening consent to perform the ImmunoProfile and OncoPanel, subjects will be presented with the option to allow their clinical outcomes to be followed, even if they do not continue on to protocol therapy. Screen-failed subjects who consented for follow-up of their clinical outcomes may have their medical records reviewed retrospectively to provide data for exploratory objectives.

5.7 Criteria for Taking a Participant Off Study

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

- Lost to follow-up
- Withdrawal by subject: Withdrawal of consent for continued follow-up
- Death

The reason for taking a subject off study, and the date the subject was removed, must be documented in the CRF. In addition, the DF/HCC study team will ensure Off Treatment and Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

6.1 Nivolumab

Recommendations for nivolumab modifications are provided in the table below.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

In subjects with mild or moderate infusion reactions, nivolumab infusion should be interrupted or slowed. In subjects with severe or life-threatening infusion reactions, nivolumab should be discontinued.

If nivolumab is held for treatment-related toxicity, docetaxel should be continued as scheduled. If the patient has not completed 6 cycles of docetaxel when nivolumab is resumed, nivolumab should be restarted with the next scheduled docetaxel infusion. If the patient has completed 6 cycles of docetaxel when nivolumab is resumed, nivolumab should be restarted at 480mg every 4 weeks.

If docetaxel is held for treatment-related toxicity, nivolumab should be held until docetaxel is resumed or discontinued.

If subjects discontinue docetaxel early for intolerability, nivolumab may be converted to 480mg every 4 weeks schedule.

If both nivolumab and docetaxel are held for intolerability, both drugs may be resumed when it is determined to be safe by the treating investigator. Treatment does not need to be restarted in 21 days from time of last administration.

Reinitiation of nivolumab monotherapy does not need to be in 21 or 28 days (e.g. 3 weeks or 4 weeks) from time of last administration.

If nivolumab is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Table 3.

Table 3. Recommended Dose Modification for Nivolumab

Adverse reaction	**Severity (CTCAE v5.0)**	**Dose Modification**
Colitis or Diarrhea	Grade 2	• Withhold dose • Resume when AE improves to Grade ≤1
	Grade 3	• Withhold dose • Resume when AE improves to Grade ≤1
	Grade 4	• Permanently discontinue
Pneumonitis	Grade 2	• Withhold dose • Resume when AE improves to Grade ≤1
	Grade 3 or Grade 4	• Permanently discontinue
Hepatitis[1]	AST or ALT >3-5 times ULN or total bilirubin >1.5-3 times ULN	• Withhold dose • Resume when AE improves to Grade ≤1
	AST or ALT >5 times ULN or total bilirubin > 3 times ULN	• Permanently discontinue
Hypophysitis	Grade 2 or 3	• Withhold dose • Resume when AE improves to Grade ≤1
	Grade 4	• Permanently discontinue
Adrenal insufficiency	Grade 2	• Withhold dose • Resume when AE improves to Grade ≤1
	Grade 3 or Grade 4	• Permanently discontinue
Type 1 diabetes mellitus	Grade 3 hyperglycemia	• Withhold dose • Resume when AE improves to Grade ≤1
	Grade 4 hyperglycemia	• Permanently discontinue
Nephritis and renal dysfunction	Serum creatinine >1.5-6 times ULN	• Withhold dose • Resume when AE improves to Grade ≤1
	Serum creatinine >6 times ULN	• Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	• Withhold dose • Resume when AE improves to Grade ≤1
	Grade 4 rash or confirmed SJS or TEN	• Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	• Withhold dose • Resume when AE improves to Grade ≤1

	Immune-mediated encephalitis	• Permanently discontinue
Other	Other Grade 3 AEs	• First occurrence: Withhold dose and resume when AE improves to Grade ≤1 • Recurrence of same Grade 3 AE: Permanently discontinue
	Life-threatening or Grade 4 AE	• Permanently discontinue
	Requirement of ≥10 mg/day prednisone or equivalent for >12 weeks	• Permanently discontinue
	Persistent Grade 2 or 3 AE lasting ≥12 weeks	• Permanently discontinue
1. For patients with liver metastasis who begin treatment with AST or ALT up to 5x ULN (up to Grade 2 AST or ALT elevation), and AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week, treatment should be discontinued.		

In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). Safety management algorithms for organ-specific AEs are found in Appendix D to serve as general guidance.

6.1.1 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3, 4, or 5 infusion reactions should be reported as a serious adverse event (SAE) if criteria are met within 24 hours to the PCCTC. The PCCTC, on behalf of the Sponsor-Investigator will report SAEs to BMS Worldwide Safety Medical Monitor within 24 hours / 1 Business Day of becoming aware of the event. Infusion reactions should be graded according to CTCAE v5.0 guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate.

Reporting requirements and responsibilities are listed in section 7.4.

Grade 1 Symptoms: Mild reaction; infusion interruption not indicated; intervention not indicated.

- Remain at bedside and monitor subject until recovery from symptoms.

- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50mg IV (or equivalent) and/or acetaminophen 325 to 1000mg administered orally at least 30 minutes before additional nivolumab administrations.

Grade 2 Symptoms: Moderate reaction; requires therapy or infusion interruptions but responds promptly to symptomatic treatment (e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids; prophylactic medications indicated for ≤ 24 hours.

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50mg IV (or equivalent) and/or acetaminophen 325 to 1000mg administered orally. Remain at bedside and monitor subject until resolution of symptoms. Corticosteroids or bronchodiliator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- The amount of nivolumab infused must be recorded on the eCRF. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50mg IV (or equivalent) and/or acetaminophen 325 to 1000mg should be administered orally at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25mg of IV hydrocortisone or equivalent) may be used.

Grade 3 or Grade 4 symptoms: Severe reaction; Grade 3: prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for the clinical sequelae (e.g. renal impairment, pulmonary infiltrate). Grade 4: life-threatening; pressor or ventilatory support indicated.

- Immediately discontinue nivolumab infusion. Begin an IV infusion of normal saline and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1mg of 1:1,000 solution for subcutaneous administration of 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50mg IV with methylprednisolone 100mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

6.2 Docetaxel

Recommendations for docetaxel modifications are provided in the tables below.

No more than two dose reductions will be allowed for an individual subject (See Table below). If docetaxel dose is reduced for toxicity, the dose will not be re-escalated back to the starting level. Docetaxel infusion may be delayed for up to 3 weeks to allow for recovery from toxicity. If treatment must be delayed for more than 3 weeks or a subject cannot tolerate a second dose reduction, docetaxel will be discontinued.

If nivolumab is held for treatment-related toxicity, docetaxel should be continued as scheduled.

If both nivolumab and docetaxel are held for intolerability, these may be resumed when it is determined to be safe by the treating investigator. Treatment does not need to be restarted in 21 days from time of last administration.

If a dose of docetaxel is missed or delayed, subjects should resume treatment with plan to complete 6 cycles of docetaxel. Reinitiation of docetaxel does not need to be done in 21 days from time of last administration.

Dose Levels for Docetaxel	
Dose level 0	75 mg/m^2
Dose level 1	65 mg/m^2
Dose level 2	55 mg/m^2

Dose modifications for docetaxel-related AE(s) should be made according to institutional standards. Recommendations are provided below for guidance.

Table 4. Recommended Dose Modification for Docetaxel

Adverse reaction	**Severity (CTCAE v5.0)**	**Dose Modification**
Hypersensitivity reaction[a]	Mild (localized cutaneous reactions e.g. mild pruritus, flushing, rash)	• Consider decreasing rate of infusion until recovery from symptoms and then complete infusion at initial rate • Closely monitor subject at bedside
	Moderate (e.g., generalized pruritus, flushing, rash, dyspnea, hypotension with SBP >80 mmHg)	• Interrupt infusion • Administer diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV (or equivalent) • Monitor until symptom resolution • Resume infusion after symptom resolution at a slower rate, and increase incrementally to initial rate (e.g., 8 hr rate for 5 min, then 4 hr rate for 5 min, then 2 hr rate for 5 min, then 1 hr infusion rate) • Depending on severity of reaction, consider additional oral or IV premedication with an antihistamine prior to subsequent cycles with decreased infusion rate initially
	Severe (e.g., bronchospasm, generalized urticaria, systolic BP	• Interrupt infusion immediately • Administer diphenhydramine 50 mg IV

Adverse reaction	Severity (CTCAE v5.0)	Dose Modification
	≤8 0mmHg, angioedema)	with or without dexamethasone 10 mg IV (or equivalent) • Administer epinephrine as clinically indicated • Monitor until symptom resolution • Depending on symptom severity, either resume infusion after symptom resolution at a slower rate, and increase incrementally to initial rate (see above) or obtain allergy consultation for desensitization for all future infusions • Depending on severity of reaction, consider additional oral or IV premedication with an antihistamine prior to subsequent cycles with decreased infusion rate initially • Permanently discontinue if 2 episodes
	Anaphylaxis (life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion)	• Permanently discontinue
Neutropenia	Grade 1	• No change
	Grade 2	• Reduce one dose level
	Grade 3 or Grade 4	• Delay dosing one week • Retreat with one dose level dose reduction once ANC recovers to ≥1500/mm^3
	Prolonged Grade 4 neutropenia or Neutropenic fever[b]	• If afebrile Grade 4 neutropenia ≥7 days or Grade ≥3 neutropenia associated with fever: Retreat with one level dose reduction once ANC recovers to ≥1500/mm^3 • If an infection is identified, the fever must have resolved and be adequately treated with clinical resolution before treatment reinitiation • If bacteremic, repeat blood culture must demonstrate clearance of bacteremia • Subjects may continue or resume chemotherapy while completing antibiotics
Thrombocytopenia	<LLN – 100,000/mm^3	• No change
	75,000 – 99,999/mm^3	• Reduce one dose level
	<75,000/mm^3	• Delay dosing one week • Retreat with one dose level dose reduction once platelet count recovers to ≥100,000/mm^3
Elevated LFTs[c]	Total bilirubin > ULN or ALT or AST > 5 times ULN	• Delay dosing ≤3 weeks • If total bilirubin recovers to within normal limits (wnl) and ALT or AST recovers to

Adverse reaction	Severity (CTCAE v5.0)	Dose Modification
		<3 times ULN, reduce dose by one dose level
	Total bilirubin ≤ ULN and ALT or AST >3 times (and ≤ 5 times) ULN	• Reduce one dose level (no treatment delay)
Stomatitis	Grade 2	• Withhold dose • Resume when stomatitis is resolved
	Grade 3 or Grade 4	• Withhold dose • Retreat with one dose level dose reduction when stomatitis is resolved • If second Grade 3-4 stomatitis, withhold dose until resolution and retreat with one more dose level dose reduction • If third Grade 3-4 stomatitis, permanently discontinue
Peripheral neuropathy	Grade 2	• Withhold dose • Retreat with one dose level dose reduction when recovers to Grade ≤1 • Permanently discontinue if neurotoxicity persists for >3 weeks
	Grade 3 or Grade 4	• Permanently discontinue
Diarrhea	Grade ≥1 diarrhea	• Initiate prophylactic loperamide or diphenoxylate with subsequent treatment • If Grade >2 diarrhea despite prophylaxis, reduce one dose level • If Grade >2 diarrhea despite prophylaxis and dose reduction, permanently discontinue
	Grade 3-4 diarrhea with concurrent Grade 3-4 neutropenia	• Hold dose until diarrhea improves to Grade ≤2 and ANC recovers to >1,000/mm^3
Other	Other Grade 1-2 AEs	• Symptomatic management • Retreat without dose reduction
	Other Grade 3 or 4 AEs	• Withhold dose if clinically significant (Exception: anemia which can be transfused) • Retreat with one dose level dose reduction when recovers to Grade ≤1

[a] There are no dose reductions for hypersensitivity reactions.
[b] Fever: defined as 1 reading of oral temperature >38.5^{o}C or 3 readings of oral temperature >38.0^{o}C over 24-hour period.
[c] For patients with liver metastasis who begin treatment with AST or ALT up to 5x ULN (up to Grade 2 AST or ALT elevation), the same recommendations for docetaxel modification apply as detailed in Table 4.

6.3 LHRH analogue

There will be no dose modifications for ADT. Dose interruptions are not allowed.

6.4 Abiraterone acetate

Recommendations for dose modifications for adverse reactions associated with abiraterone acetate are provided in the tables below.

Adverse reaction	Severity (CTCAE v5.0)	Dose Modification
Elevated LFTs[a]	Grade 1 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT from ULN to 2.5X ULN; increase in total bilirubin from ULN to 1.5X ULN)	• Increase frequency of LFT monitoring to at least weekly, if investigator judges that the laboratory abnormalities are potentially related to abiraterone • No dose reduction is required • If LFTs are stable for 4 weeks, resume monthly monitoring
	Grade 2 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to 2.5-5X ULN; increase in total bilirubin from 1.5-3X ULN)	Hold abiraterone and other concomitant medications that are potentially hepatotoxic. • Increase frequency of LFT monitoring to at least weekly until LFTs return to baseline or Grade 1when abiraterone can be restarted • No dose reduction is required after 1 episode providing this resolved within 4 weeks, but should be considered if Grade 1 abnormalities recur
	Grade 3 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >5-20X ULN; increased in total bilirubin to >3-10X ULN)	• Hold abiraterone and other concomitant medications that are potentially hepatotoxic • Increase frequency of LFT monitoring to at least weekly until LFTs return to baseline or Grade 1 • If abiraterone reinitiation is considered and the PI agrees, restart with first DL reduction (750mg) when Grade 3 toxicities return to baseline or Grade 1. Patients who restart treatment should have LFTs monitored at a minimum of every 2 weeks for 3 months, and monthly thereafter
	Grade 4 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >20x ULN; increase in total bilirubin to >10x ULN)	• Patients must discontinue abiraterone immediately. • At least weekly LFT monitoring until LFTs return to baseline or Grade 1, and then Prednisone can be discontinued. • Abiraterone should not be re-introduced
	Re-challenge for recurrent Grade 2 AST, ALT or bilirubin elevation	• Once LFTs return to baseline or Grade 1, reduce abiraterone to 750mg daily
	Re-challenge for Grade 3 AST,	• If abiraterone resumption is considered,

Adverse reaction	Severity (CTCAE v5.0)	Dose Modification
	ALT or bilirubin elevation	resume with abiraterone dose reduction to 750mg daily when LFTs return to baseline or Grade 1
	Re-challenge for recurrent Grade 3 or higher AST, ALT or bilirubin elevation after first dose reduction	• Patients must discontinue abiraterone immediately. • At least weekly LFT monitoring until LFTs return to baseline or Grade 1 • If abiraterone resumption is considered, resume with abiraterone dose reduction to 500mg daily when LFTs return to baseline or Grade 1
Hypertension[b]	Grade 1 or Grade 2	• Manage per investigator with anti-hypertensive treatment and increasing frequency of blood pressure monitoring to at least weekly. • Follow local guidance for selection of anti-hypertensives but avoid thiazide diuretics to minimize risk of serum potassium derangement. Calcium channel antagonists or beta blockers are often preferred. • For patients on prednisone 5mg daily, consider increasing prednisone dose to 5mg BID.
	Grade 3 or Grade 4	• Hold abiraterone. • Adjust or add anti-hypertensive medications to mitigate the toxicity. • When hypertension improves to Grade ≤1, resume abiraterone at full dose with prednisone 5mg bid.
Hypokalemia	Grade 1	• Supplement with oral potassium and monitor closely • For patients on prednisone 5mg daily, increase prednisolone dose to 5mg BID • Exclude and manage other causes of hypokalemia
	Grade 2	• Hold abiraterone • Supplement with oral potassium and monitor closely • For patients on prednisone 5mg daily, increase prednisolone dose to 5mg BID • Exclude and manage other causes of hypokalemia • When potassium level returns to baseline or Grade 1, re-start abiraterone with close monitoring, discontinue if recurs
	Grade 3 or Grade 4	• Permanently discontinued abiraterone • Hospitalization for IV potassium replacement and cardiac monitoring
Fluid retention or	Grade 1 or Grade 2	• For patients on prednisone 5mg daily,

Adverse reaction	Severity (CTCAE v5.0)	Dose Modification
edema		increase prednisolone dose to 5mg BID
	Grade 3 or Grade 4	• Hold abiraterone • Consider adding mineralocorticoid receptor antagonist Eplerenone until symptoms resolve • When fluid retention/edema returns to baseline or Grade 1, resume abiraterone at full dose with prednisone 5mg bid • If symptoms do not resolve or return to Grade 1, abiraterone should not be restarted
Diarrhea	Grade 1 or Grade 2	• Symptomatic management per investigator
	Grade 3 or Grade 4	• Hold abiraterone • When symptoms returns to baseline or Grade 1, resume abiraterone at 750mg daily
[a] Consider hepatology consult or opinion if there are any concerns or LFT derangements show no improvement within 2 weeks after discontinuation of abiraterone. [b] Consider cardiology consult or opinion if blood pressure control is not achieved within 4 weeks.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Serious Adverse Events: Definition

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical,

surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy and potential drug-induced liver injury (DILI) is not always serious by regulatory definition, these events must be reported within the SAEs timeline.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

- All SAEs that occur following the subject's initial dose of study treatment through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).
- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

An appropriate SAE form (e.g., USA = MedWatch form) should be used to report SAEs.

7.2 Expected Toxicities

7.2.1 Adverse Events Lists

7.2.1.1 Adverse Event List for Nivolumab

Overall, the safety profile of nivolumab monotherapy in subjects with cancer is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1-2) with relatively few drug-related high-grade (Grade 3-4) AEs. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone.

Table 5. Adverse Event List for Nivolumab

Infections and infestations	
Common	Upper respiratory tract infection
Uncommon	Pneumonia[a], bronchitis
Rare	aseptic meningitis[h]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	Lymphopenia[a], Anemia[b,j], Leucopenia[b], Thrombocytopenia[b], Neutropenia[a,b]
Uncommon	Eosinophilia
Not known	haemophagocytic lymphohistiocytosis
Immune system disorders	
Common	Infusion related reaction[c], hypersensitivity (including anaphylactic reaction)[c]
Uncommon	Sarcoidosis
Not known	Solid organ transplant rejection[g]
Endocrine disorders	
Common	Hypothyroidism, hyperthyroidism, thyroiditis
Uncommon	Adrenal insufficiency, hypopituitarism, hypophysitis, diabetes mellitus
Rare	Diabetic ketoacidosis, hypoparathyroidism
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycemia[b,c], hypoglycemia[b]
Common	Dehydration, weight decreased
Uncommon	Metabolic acidosis
Not known	tumor lysis syndrome[h]
Hepatobiliary disorders	
Uncommon	Cholestasis, Hepatitis[c]
Nervous system disorders	
Very common	Headache
Common	Peripheral neuropathy, dizziness
Uncommon	Polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)

Rare	Guillain-Barre syndrome, demyelination, myasthenic syndrome, encephalitis[a,c,l]
Eye disorders	
Common	Blurrend vision, dry eye
Uncommon	Uveitis
Not known	Vogt-Koyanagi-Harada syndrome[g]
Cardiac disorders	
Common	Tachycardia, atrial fibrillation
Uncommon	Myocarditis[a,e], pericardial disorders[j], arrhythmia (including ventricular arrhythmia)[d]
Vascular disorders	
Common	Hypertension
Rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	Dyspnea[a], cough
Common	Pneumonitis[a,c], Pleural effusion
Uncommon	Lung infiltration
Gastrointestinal disorders	
Very common	Diarrhea, nausea, vomiting, abdominal pain, constipation
Common	Colitis[a], stomatitis, dry mouth
Uncommon	Pancreatitis, gastritis
Rare	Duodenal ulcer
Skin and subcutaneous tissue disorders	
Very common	Rash[d], pruritus
Common	Vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	Erythema multiforme, psoriasis, rosacea
Rare	Toxic epidermal necrolysis[a,e], Stevens-Johnson syndrome[a]
Not known	Lichen sclerosus[h], other lichen disorders
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain[f], arthralgia
Common	Arthritis
Uncommon	Polymyalgia rheumatica
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a], rhabdomyolysis[a,c]
Renal and urinary disorders	
Common	Renal failure (including acute kidney injury)[a,c]
Rare	Tubulointerstitital nephritis, cystitis noninfective[h]
General disorders and administration site conditions	
Very common	Fatigue, pyrexia, edema[m]
Common	Pain, chest pain
Laboratory investigations[b]	
Very common	Increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcemia, increased creatinine, hypercalcemia, hyperkalaemia, hypokalemia, hypomagnesemia
Common	Increased total bilirubin, hypermagnesemia, hypernatremia
Very common (≥1/10); Common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000) [a] Fatal cases have been reported in completed or ongoing clinical studies.	

[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.
[c] Life-threatening cases have been reported in completed or ongoing clinical studies.

[d] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.
[e] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
[f] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
[g] Post-marketing event (also see section 4.4).
[h] Reported in clinical studies and in the post-marketing setting.
[i] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.
[j] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia.
[k] Includes adrenal insufficiency, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency
[l] Includes encephalitis and limbic encephalitis
[m] Edema is a composite term which includes generalized edema, edema peripheral, peripheral swelling and swelling

Refer to the nivolumab Investigator's Brochure for the comprehensive list of AEs.

7.2.1.2 **Adverse Event List for Docetaxel**

The most common AEs across all docetaxel indications are:

- Infections
- Neutropenia
- Anemia
- Febrile neutropenia
- Hypersensitivity
- Thrombocytopenia
- Neuropathy
- Dysgeusia
- Dyspnea
- Constipation
- Anorexia
- Nail disorders
- Fluid retention
- Asthenia
- Pain
- Nausea
- Diarrhea
- Vomiting
- Mucositis

- Alopecia
- Skin reactions
- Myalgia

Refer to the docetaxel package insert for the comprehensive list of AEs.

7.2.1.3 **Adverse Event List for LHRH Analogue**

The most common AEs observed with LHRH analogue agents are:
- Vasomotor hot flashes
- Edema
- Gynecomastia
- Bone pain
- Thrombosis
- Gastrointestinal disturbances

Other AEs include:
- Impotence
- Loss of libido
- Weight gain
- Depression
- Dizziness
- Anemia
- Skin reactions
- Pain at injection site
- Taste perversion
- Dry mouth
- Thirst
- Decrease in bone density

Refer to the respective LHRH analogue package insert for the comprehensive list of AEs.

7.2.1.4 **Adverse Event List for Abiraterone Acetate**

The most common adverse reactions (≥10%) observed with abiraterone acetate include:
- Fatigue
- Arthralgia
- Hypertension
- Nausea
- Edema
- Hypokalemia
- Hot flush
- Diarrhea
- Vomiting
- Upper respiratory infection
- Cough

- Headache

The most common laboratory abnormalities (>20%) observed with abiraterone acetate include:
- Anemia
- Elevated alkaline phosphatase
- Hypertriglyceridemia
- Lymphopenia
- Hypercholesterolemia
- Hyperglycemia
- Hypokalemia

Refer to the abiraterone acetate package insert for the comprehensive list of AEs.

7.3 Adverse Event Characteristics

- AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)
- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported by DF/HCC to the DF/HCC IRB if the AE varies in nature, intensity or frequency from the expected toxicity information which is provided. Participating sites should see details in section 7.4 for AE reporting requirements.

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

7.4 Adverse Event Reporting

7.4.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Sponsor-Investigator.

7.4.2 Investigators **must** report to the Sponsor-Investigator any SAE that occurs after the initial dose of study treatment, during treatment, or within 100 days of the last dose of treatment on the local institutional AE form or other study-approved form (i.e., MedWatch form).

7.4.3 For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor-Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected Grade 2 or Grade 3 with a possible, probable or definite attribution, unexpected Grade 4 toxicities, and Grade 5 (death) regardless of study phase or attribution. This requirement is in addition to reporting requirements for serious AEs. AEs/SAEs requiring reporting should be reported based on the shortest reporting requirement timeframe.

7.4.4 **DF/HCC Adverse Event Reporting Guidelines**

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

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting AEs, in addition to reporting to the PCCTC per DF/HCC requirements. A copy of the participating site AE form (or MedWatch form) should be forwarded to the PCCTC within the timeframes detailed in the table below.

Table 6. Timeframes for Reporting Adverse Events

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

The Sponsor-Investigator will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting AEs.

7.4.5 Site Responsibilities

Sites are responsible for reporting AEs to the PCCTC per Table 6 and all SAEs to the PCCTC within 24 hours or 1 business day.

PCCTC:
Prostate Cancer Clinical Trials Consortium

Email: pcctc@mskcc.org

7.4.5.1 Reporting to Hospital Risk Management

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

7.4.5.2 Routine Adverse Event Reporting

All AEs **must** be reported in routine study data submissions on the toxicity case report forms. **AEs reported through expedited processes (e.g., via MedWatch, etc.) must <u>also</u> be reported in routine study data submissions.**

7.4.6 Sponsor-Investigator's Responsibilities

Reporting to the Food and Drug Administration (FDA) and Bristol-Myers Squibb (BMS).

The Sponsor-Investigator, as overall PI, will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any SAE that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

The PCCTC, on behalf of the Sponsor-Investigator will report SAEs to BMS. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours / 1 Business Day of becoming aware of the event. SAEs must be recorded on MedWatch, or approved site SAE form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 business day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE, defined as definite, probable or possible in attribution (Section 7.2).

Not related: There is not a reasonable causal relationship between study drug administration and the AE, defined as unlikely or unrelated in attribution (Section 7.2).

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.5 AE Reconciliation

The PCCTC, on behalf of the Sponsor-Investigator, will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

- The PCCTC will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the PCCTC the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the PCCTC determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

7.6 External Safety Reports

In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.
- ✓ Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB for the study, the sponsor will submit the ESR to the appropriate IRB as required by that IRB. The investigator and IRB will determine if the informed consent requires revision. The

investigator should also comply with the IRB procedures for reporting any other safety information.

7.7 Nonserious Adverse Events

- Non-serious AEs are to be provided to BMS by the Sponsor-Investigator in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from initiation of study drug.

7.7.1 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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

7.7.2 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

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

7.8 Pregnancy

Any pregnancy that occurs in a female partner of a male study subject should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female

partner, the female partner must sign an informed consent form for disclosure of this information.

8. PHARMACEUTICAL INFORMATION

A list of the AEs and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 Nivolumab

8.1.1 Description

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

Pharmacokinetics
The pharmacokinetics (PK) of nivolumab is linear in the dose range of 0.1 to 10 mg/kg. The geometric mean clearance (CL), terminal half-life, and average exposure at steady state at 3 mg/kg every 2 weeks of nivolumab were 7.9 mL/h, 25.0 days, and 86.6 μg/mL, respectively, based on a population PK analysis.

Nivolumab CL increased with increasing body weight. Body weight normalized dosing produced approximately uniform steady-state trough concentration over a wide range of body weights (34-162 kg).

Drug interaction
As monoclonal antibodies are not metabolized by cytochrome P450 (CYP) enzymes or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab. Therefore, pharmacokinetic interaction studies have not been conducted with nivolumab.

8.1.2 Form

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. Nivolumab injection for intravenous infusion is supplied in single-dose vials. Each mL of nivolumab solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

Nivolumab will be supplied by Bristol-Myers Squibb in 100mg/10mL single-dose vials.

8.1.3 **Storage and Stability**

Before preparation for infusion
Store nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake. The shelf-life of an unopened vial is 3 years.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

After preparation for infusion
From a microbiological point of view, the product should be used immediately. If not used immediately, chemical and physical in-use stability of nivolumab has been demonstrated for 24 hours at 2ºC to 8ºC protected from light and a maximum of 8 hours at 20°C-25°C and room light (this 8-hour period of the total 24 hours should be inclusive of the product administration period).

Refer to the latest nivolumab Investigator's Brochure (IB) for detailed information on storage and stability.

8.1.4 **Compatibility**

Nivolumab must not be mixed with other medicinal products. Nivolumab should not be infused concomitantly in the same intravenous line with other medicinal products.

Refer to the latest nivolumab Investigator's Brochure (IB) for detailed information on compatibility.

8.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 **Availability**

Nivolumab will be supplied by Bristol-Myers Squibb, and will be free of charge to subjects for this study.

8.1.7 **Preparation**

Dose calculation
The nivolumab dose for the subject is 360mg (first 6 Q3W cycles) or 480 mg (subsequent Q4W cycles). More than one vial of nivolumab concentrate may be needed to give the total flat dose for the subject.

The volume of nivolumab concentrate to prepare the 360mg dose (mL) = 36 mL.

The volume of nivolumab concentrate to prepare the 480mg dose (mL) = 48 mL.

Preparing the infusion
Take care to ensure aseptic handling when you prepare the infusion.

Nivolumab can be used for intravenous administration either:
- Without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- After diluting to concentrations as low as 1mg/mL. The final infusion concentration should range between 1 and 10 mg/mL. Nivolumab concentrate may be diluted with either:
    - Sodium chloride 9 mg/mL (0.9%) solution for injection; or
    - 50 mg/mL (5%) glucose solution for injection.

STEP 1
- Inspect the nivolumab concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab concentrate is a clear to opalescent, colorless to pale yellow liquid. Discard the vial if the solution is cloudy, is discolored, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of nivolumab concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

Refer to the latest nivolumab Investigator's Brochure (IB) for detailed information on preparation.

8.1.8 **Administration**

Nivolumab infusion must not be administered as an IV push or bolus injection. Administer nivolumab infusion intravenously over a period of 30 minutes. Nivolumab infusion should not be infused at the same time in the same intravenous line with other agents.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm). Nivolumab infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Disposal
Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

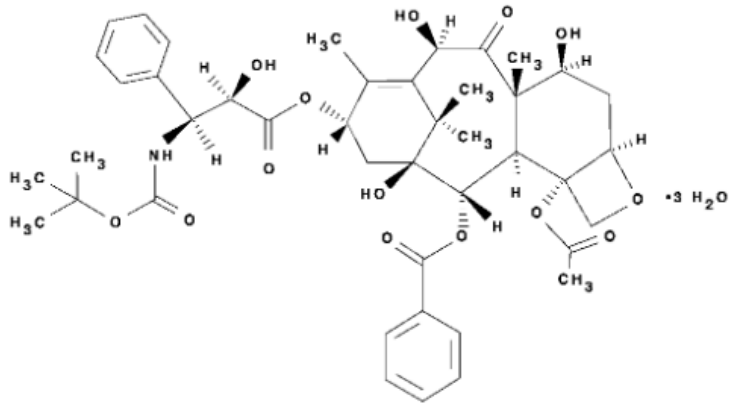
8.1.9 **Ordering**

The study site will order the nivolumab product from Bristol-Myers Squibb.

8.2 Docetaxel

8.2.1 **Description**

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}•3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

Pharmacokinetics
Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the

peripheral compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 (see Drug Interactions below).

Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

Drug interactions
Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

After completion of docetaxel chemotherapy (Cycle 1-6), CYP3A4 medications may be restarted at least 1 week after the last docetaxel administration.

8.2.2 **Form**

Docetaxel Injection Concentrate is a clear yellow to brownish-yellow viscous solution. Docetaxel is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5mL) or 80 mg (2mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

Docetaxel Injection Concentrate requires dilution with Diluent prior to addition to the infusion bag. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for Docetaxel contains 13% ethanol in water for injection and is supplied in vials.

Two-vial formulations (injection concentrate and diluent):

1. Docetaxel 80 mg/2 mL (Docetaxel injection concentrate 80 mg/2 mL): 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for docetaxel 80 mg (13% w/w ethanol in water for injection). Both items are in a blister pack in one carton.

2. Docetaxel 20 mg/0.5 mL (Docetaxel injection concentrate 20 mg/0.5 mL): 20mg docetaxel in 0.5 mL polysorbate 80 and Diluent for docetaxel 20 mg (13% w/w ethanol in water for injection). Both items are in a blister pack in one carton.

Docetaxel is commercially available.

8.2.3 **Storage and Stability**

Store docetaxel between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Docetaxel final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. Docetaxel final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour IV administration). The storage and preparation of docetaxel will be per institutional standards.

8.2.4 **Compatibility**

Docetaxel should be diluted in either 0.9% Sodium Chloride solution or 5% Dextrose solution. Docetaxel should not be infused concomitantly in the same intravenous line with other medicinal products.

8.2.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.6 **Availability**

Docetaxel is commercially available and will not be provided free of charge for this study.

8.2.7 **Preparation**

<u>Two-vial formulation (Injection Concentrate and Diluent)</u>

A. Initial Diluted Solution
   1. Docetaxel vials should be stored between 2°C and 25°C (36°F and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of docetaxel Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.
   2. Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.8 mL for docetaxel 20 mg and approximately 7.1 mL for docetaxel 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of docetaxel Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/mL will result.

3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process. The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Product	Diluent (13% w/w ethanol in water for injection) Fill Range (mL)	Approximate extractable volume of Dilutent when entire contents are withdrawn (mL)	Concentration of the initial diluted solution (mg/mL docetaxel)
Docetaxel 20 mg/0.5 mL	1.88-2.08 mL	1.8 mL	10 mg/mL
Docetaxel 80 mg/2 mL	6.96-7.70 mL	7.1 mL	10 mg/mL

B. Final Dilution for Infusion
1. Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel initial diluted solution or final dilution for IV infusion is not clear or appears to have precipitation, these should be discarded

8.2.8 **Administration**

Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

The final docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

8.2.9 **Ordering**

Docetaxel is commercially available. The site Director of Pharmacy and/or the site research pharmacy should ensure that docetaxel is in stock in their investigative site. If docetaxel is not stocked, the agent should be ordered before the protocol is activated.

8.3 LHRH Analogue

LHRH analogues (e.g., leuprolide, goserelin acetate, and degarelix) are synthetic long-acting analogs of the native LHRH peptide that possess greater potency than the natural hormone.

LHRH analogues are FDA approved for the treatment of metastatic prostate cancer and are administered using a variety of techniques (e.g., intramuscular for leuprolide, subcutaneous for goserelin acetate and degarelix).

LHRH analogues are commercially available and will not be provided free of charge for this study. The site Director of Pharmacy and/or the site research pharmacy should ensure that these agents are in stock in their investigative site. If not stocked, the agents should be ordered before the protocol is activated.

The storage, handling, preparation, and administration of LHRH analogues will be per institutional standards in this study. Please refer to FDA approved package inserts for additional information.

8.4 Abiraterone Acetate

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

Abiraterone acetate is FDA approved for the treatment of metastatic hormone sensitive prostate cancer as well as metastatic hormone resistant prostate cancer. Abiraterone acetate is administered orally at a dose of 1,000mg daily in combination with prednisone 5mg daily or BID (Refer to FDA approved package insert for additional information).

Abiraterone acetate is commercially available and will not be provided free of charge for this study. The site Director of Pharmacy and/or the site research pharmacy should ensure that these agents are in stock in their investigative site. If not stocked, the agents should be ordered before the protocol is activated.

The storage, handling, preparation, and administration of abiraterone acetate will be per institutional standards in this study. Please refer to the abiraterone FDA approved package insert for additional information.

9. BIOMARKER AND CORRELATIVE STUDIES

9.1 Biomarker Studies

Subjects with a tumor that harbors DNA repair defect(s) or an inflamed tumor microenvironment by CD8 or PD-L1 staining will be prospectively enriched using the OncoPanel and ImmunoProfile assays, respectively. OncoPanel and ImmunoProfile are integral assays required

for proper cohort allocation. See Section 2.5.3 (Rationale for Prospective Biomarker-Based Patient Selection).

Table 7. Biomarker Studies

	OncoPanel	**ImmunoProfile**
Bioassays type	Next generation sequencing (Integral)	Multiplex immunofluorescence (Integral)
CLIA-certified laboratory	Yes	Yes before October 2022. No after October 2022.
Laboratory (DFCI/BWH)	Center for Advanced Molecular Diagnostics	Tissue Biomarker Laboratory of the Center for Immuno-Oncology
Tissue type	(1) prostate biopsy, (2) TURP tissue, (3) TURBT tissue with contiguous spread of prostate cancer to the bladder, or (4) metastatic biopsy tissue (excluding tissue from bone and lymph node biopsies)	
Tissue requirement	At least ten (10) 5-micron FFPE slides + 1 adjacent H&E slide; each slide must contain ≥20% tumor If unavailable, a lower number of 4-micron or 5-micron slides and/or slides containing lower tumor involvement may be accepted after discussion with the Sponsor-Investigator.	At least one (1) 5-micron FFPE slide + 1 adjacent H&E slide; slide must contain ≥50% tumor If unavailable, a 5-micron slide containing lower tumor involvement may be accepted after discussion with the study Sponsor-Investigator.
Integral biomarkers	DDR defects	CD8 and PD-L1 expression
Anticipated turnaround time*	4 weeks	2-4 weeks
*From receipt of FFPE slides by laboratory to availability of bioassay results.		

9.1.1 **OncoPanel**

Background

Somatic genetic alterations in oncogenes and tumor-suppressor genes contribute to the pathogenesis and evolution of human cancers. These alterations can provide prognostic and predictive information and stratify cancers for targeted therapeutic information. Alterations are classified into five tiers using the following guidelines:

Tier 1: The alteration has well-established published evidence confirming clinical utility in this tumor type, in at least one of the following contexts: predicting response to treatment with an FDA-approved therapy; assessing prognosis; establishing a definitive diagnosis; or conferring an inherited increased risk of cancer to this patient and family.

Tier 2: The alteration may have clinical utility in at least one of the following contexts: selection of an investigational therapy in clinical trials for this cancer type; limited evidence of prognostic association; supportive of a specific diagnosis; proven association of response to treatment with an FDA-approved therapy in a different type of cancer; or similar to a different mutation with a proven association with response to treatment with an FDA-approved therapy in this type of cancer.

Tier 3: The alteration is of uncertain clinical utility, but may have a role as suggested by at least one of the following: demonstration of association with response to treatment in this cancer type in preclinical studies (e.g., in vitro studies or animal models); alteration in a biochemical pathway that has other known, therapeutically-targetable alterations; alteration in a highly conserved region of the protein predicted, in silico, to alter protein function; or selection of an investigational therapy for a different cancer type.

Tier 4: The alteration is novel or its significance has not been studied in cancer.

Tier 5: The alteration has been determined to have no clinical utility, either for selecting therapy, assessing prognosis, establishing a diagnosis, or determining hereditary disease risk.

Insufficient Coverage: If specified exon(s) have <50X coverage, that gene for that specific exon is considered to have insufficient coverage

Pertinent Negative: Specified exon(s) or codon(s) of interest for the given panel having sufficient coverage and no variants found.

Copy Count Estimation: When the estimated number of copies for a CNV (copy number variation) call is calculated as ≥ 6 copies, the report will include the number of copies instead of reporting high or low amplification. The copy estimate is the average number of copies in the sample and is not adjusted for subclonal events, rounded to the nearest whole number. IMPORTANTLY, the estimated copy number is a function of the subjective visual assessment of tumor purity (heterogeneity) made by a pathologist. As such, this copy number is an estimate, with an element of error. Copy number alterations are called at the gene level; genes that are not on our assay but are present in the cytoband should not have the same copy alteration inferred.

Tumor mutational burden (TMB): TMB is calculated by determining the number of non-synonymous somatic mutations that occur per megabase of exonic sequence data across all genes on the panel. Measurement of tumor mutational burden may be less precise in tumors with very low tumor involvement and can potentially be affected by the presence of rare germline variants that are not removed by population allele frequency-based filtering. The tumor mutational burden for a case is reported as a percentile in relation to all prior Profile clinical and research cohort samples sequenced on the current version of Oncopanel, as well as a percentile in relation to all tumors of that specific type. A tumor type-specific percentile is not provided for tumor types that have cumulatively been sequenced less than 10 times due to insufficient data for meaningful comparison.

Mismatch repair pathway status: MMR pathway is evaluated by determining the number of small insertion/deletion events that occur in homopolymer regions within exonic sequence data across all genes on the panel, using an extension of a method previously developed in our laboratory (J Mol Diagn. 2017;19(1):84-91). Tumors with an elevated number of such events are classified as mismatch repair deficient (MSI-H), while tumors with a low burden of such events are classified as mismatch repair proficient (MSS). In some cases, it may be not be possible

to make a definitive determination about mismatch repair pathway status. This may be due multiple factors, including low tumor involvement, suboptimal sequence quality, and the presence of another mutational signature. For these indeterminate cases, orthogonal testing via

immunohistochemistry for mismatch repair protein expression or microsatellite instability testing by PCR should be considered.

Mutational signature analysis: For tumors with 16 or more mutations, additional mutational signature analysis is performed based upon the pattern of nucleotide substitutions. Mutational signatures that can be detected using this approach include those associated with DNA damage due to ultraviolet light (UVA) exposure, tobacco smoke exposure, prior treatment with alkylating agents (including temozolomide), impaired POLE DNA polymerase function, and APOBEC enzyme dysregulation. The OncoPanel mutational signature detection tool is based upon previously published signatures derived from whole exome sequencing data (Alexandrov et al. Nature 500:415-21 (2013)), and was refined by training on targeted exome sequencing data (Zehir et al. Nature Medicine 23, 703–713 (2017)). The reported mutational patterns reflect those observed in vitro following exposure to relevant mutagens. The presence of these signatures, as detected by the OncoPanel mutational signature tool, was further validated against clinicopathologic features in 738 OncoPanel samples including (1) origin at a sun-exposed site, (2) smoking history, (3) prior treatment with temozolomide, (4) concurrent POLE hotspot mutation, or (5) MMR deficiency as detected by OncoPanel. Mutational signature sensitivity ranges from 42 to 82% and specificity from 80 to > 99% relative to matched clinical features. However, extensive functional analysis has not been performed for validation and, therefore, these signatures should be interpreted as observed patterns consistent with the appropriate pathologic mechanism, but not definitive assertions. Failure to detect a mutational signature despite a relevant clinical context may result from low numbers of mutations identified by this targeted assay, low tumor involvement, and/or alternative mechanisms of tumorigenesis.

Methodology

OncoPanel is developed as a cancer genomic assay to detect somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen or formalin-fixed paraffin-embedded samples. The OncoPanel assay surveys exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. While the genes targeted by OncoPanel remain unchanged, additional hybridization probes have been included to improve structural variant detection.

The 447 genes are: *ABCB11, ABL1, ACVR1, AKT1, AKT2, AKT3, ALK, APC, AR, ARAF, ARHGAP35, ARHGEF12, ARID1A, ARID1B, ARID2, ASXL1, ATM, ATR, ATRX, AURKA, AURKB, AXIN2, AXL, B2M, BABAM1, BAP1, BARD1, BCL11B, BCL2, BCL2L1, BCL2L12, BCL6, BCOR, BCORL1, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRCC3, BRD3, BRD4, BRE, BRIP1, BUB1B, C17ORF70, C19ORF40, C1ORF86, CALR, CARD11, CASP8, CBFA2T3, CBFB, CBL, CBLB, CCND1, CCND2, CCND3, CCNE1, CD274, CD79B, CDC73, CDH1, CDH4, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK1, CHEK2, CIC, CIITA, COL7A1, CREBBP, CRKL, CRLF2, CRTC1, CSF3R, CTCF, CTLA4, CTNNA1, CTNNB1, CUX1, CXCR4, CYLD, DAXX, DCLRE1C, DDB1, DDB2, DDR2, DICER1, DIS3, DIS3L2, DKC1, DMC1, DNMT3A, DOCK8, EGFR, EGLN1, ELANE, EME1, ENG, EP300, EPCAM, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, ERG, ESR1, ETV1, ETV4, ETV5, ETV6, EWSR1, EXO1, EXT1, EXT2, EZH2, FAH, FAM175A, FAM46C, FAN1, FANCA, FANCB, FANCC, FANCD2, FANCE,*

FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT1, FLT3, FLT4, FOXA1, FOXL2, FUS, GALNT12, GATA2, GATA3, GATA4, GATA6, GBA, GEN1, GLI1, GLI2, GNA11, GNAQ, GNAS, GPC3, GREM1, H19, H3F3A, H3F3B, HABP2, HELQ, HFE, HIST1H3B, HIST1H3C, HMBS, HNF1A, HOXB13, HRAS, ID3, ID4, IDH1, IDH2, IGF1R, IGF2, IKZF1, IL7R, ITK, JAK1, JAK2, JAK3, JAZF1, KAT6A, KAT6B, KCNQ1, KDM5A, KDM5C, KDM6A, KDR, KEAP1, KIF1B, KIT, KLF2, KLF4, KLLN, KMT2A, KMT2D, KRAS, LIG4, LMO1, LMO2, MAF, MAFB, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAPK1, MAX, MBD4, MCL1, MCM8, MDM2, MDM4, MECOM, MED12, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11A, MSH2, MSH6, MTA1, MTAP, MTOR, MUS81, MUTYH, MYB, MYBL1, MYC, MYCL1, MYCN, MYD88, NBN, NEIL1, NEIL2, NEIL3, NF1, NF2, NFE2L2, NFKBIA, NFKBIE, NFKBIZ, NKX2-1, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NPM1, NR0B1, NRAS, NRG1, NSD1, NT5C2, NTHL1, NTRK1, NTRK2, NTRK3, OGG1, PALB2, PARK2, PAX5, PAXIP1, PBRM1, PDCD1LG2, PDGFRA, PDGFRB, PHF6, PHOX2B, PIK3C2B, PIK3CA, PIK3R1, PIM1, PML, PMS1, PMS2, PNKP, POLB, POLD1, POLE, POLH, POLQ, POT1, PPARG, PPM1D, PPP2R1A, PRDM1, PRF1, PRKAR1A, PRKCI, PRKDC, PRSS1, PTCH1, PTEN, PTK2B, PTPN11, PTPN14, PVRL4, QKI, RAC1, RAD21, RAD50, RAD51, RAD51C, RAD51D, RAD52, RAD54B, RAF1, RARA, RASA1, RB1, RBBP8, RBM10, RECQL4, REL, RELA, RET, RHBDF2, RHEB, RHOA, RHOH, RHOT1, RICTOR, RIF1, RINT1, RIT1, RMRP, RNF43, RNF8, ROS1, RPA1, RPTOR, RSPO2, RSPO3, RUNX1, RUNX1T1, SBDS, SDHA, SDHAF2, SDHB, SDHC, SDHD, SERPINA1, SETBP1, SETD2, SF3B1, SH2B3, SH2D1A, SLC25A13, SLC34A2, SLX1A, SLX1B, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMARCE1, SMC3, SMO, SOCS1, SOS1, SOX2, SOX9, SPOP, SRSF2, SRY, SS18, STAG2, STAT3, STAT6, STK11, SUFU, SUZ12, TAL1, TAL2, TAZ, TCEB1, TCF3, TCF7L2, TDG, TERC, TERT, TET1, TET2, TFE3, TLX3, TMEM127, TMPRSS2, TNFAIP3, TOPBP1, TP53, TP53BP1, TRAF3, TRAF7, TRIM37, TSC1, TSC2, TSHR, U2AF1, UBE2T, UIMC1, UROD, USP28, USP8, VEGFA, VHL, WAS, WHSC1, WHSC1L1, WRN, WT1, XPA, XPC, XPO1, XRCC1, XRCC2, XRCC3, XRCC4, XRCC5, XRCC6, YAP1, ZNF217, ZNRF3, ZRSR2

191 regions across the following 60 genes are targeted for rearrangement detection: *ABL1, ALK, BCL6, BIRC3, BRAF, CBFB, CIC, CIITA, CRTC1, CRTC3, EGFR, ERG, ESR1, ETV4, ETV5, ETV6, EWSR1, FGFR1, FGFR2, FGFR3, FIP1L1, FOXO1, FUS, JAK2, KMT2A, MET, MYB, MYBL1, NAB2, NCOA2, NPM1, NR4A3, NRG1, NTRK1, NTRK2, NTRK3, NUP214, NUTM1, PDGFB, PDGFRA, PDGFRB, PHF1, PML, PPARG, RAF1, RARA, RELA, RET, ROS1, RSPO2, RSPO3, RUNX1, SLC34A2, SS18, SUZ12, TMPRSS2, TP53, WWTR1, YAP1, YWHAE*

These tests were developed and their performance characteristics determined by the Molecular Diagnostics Laboratory, Brigham and Women's Hospital. They have not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

This test is performed in a clinical laboratory that is certified by CLIA, under CLIA guidelines for clinical testing. The study results will be released to subjects because results may influence management decisions, including considerations for genetic counseling as well as considerations for targeted therapy in the future.

Study-Specific Biomarker Selection and Cohort Allocation

Subjects whose tumors harbor somatic or germline homozygous deletions and/or deleterious mutations in a DDR gene using OncoPanel will be assigned to Cohort 1, regardless of ImmunoProfile results.

DDR genes include and are not limited to *BRCA2, ATM, CHEK2, BRCA1, PALB2, RAD51D, ATR, NBN, PMS2, GEN1, MLH1, MSH2, MSH6, RAD51C, MRE11A, BRIP1, FAM175A, and CDK12.*

Deleterious mutations are defined as loss of function, splice site, nonsense, or frameshift mutations. Tumors identified as MMR-d or MSI-H will also be included in Cohort 1.

Tumors with DDRD or MMR-d/MSI-H identified in another CLIA-certified laboratory (e.g., Foundation Medicine) may be assigned to Cohort 1 after discussion with the Sponsor-Investigator. If archival tissue is available, they will be requested for OncoPanel testing; however, results will not influence eligibility. Subjects whose prescreening is unsuccessful for cohort allocation or whose biomarker status matches that of a filled cohort will not be eligible for protocol therapy.

9.1.2 **Immunoprofile**

Background

The ImmunoProfile test identifies the expression of immune-regulatory proteins within the tumor micro-environment, which includes tumor cells and tumor associated immune cells such as macrophages, dendritic cells, and T-cells. Specifically, the test measures the percentage and number of each cell type in a patient sample that is positive for the selected immune-regulatory proteins. Retrospective studies have shown that these results, in combination with the patient's cancer type, can help predict response to specific immunotherapies. It is hypothesized that this knowledge can be used prospectively to determine what therapies might work for a patient vs. not and to select the most beneficial clinical trial for a patient.

Methodology

ImmunoProfile uses multiplex immunofluorescent staining and imaging. Multiplex technology uses multiple colors to identify different cells and proteins at the same time on the same slide. Once multiplex staining is complete, the Vectra/Polaris imager will be used to acquire an image of the slide/staining for analysis. Image analysis software will then be used to determine the number and percentage of cells positive for the selected immuno-regulatory proteins. Compared to existing technology used for clinical testing today, the ImmunoProfile MIF platform is believed to provide greater sensitivity (testing for multiple proteins), specificity (using different colors to identify different cells), and accuracy (providing a quantitative measurement of positive response).

The current version of ImmunoProfile tests for 5 different proteins/markers on one slide (i.e., DAPI, a tumor marker, PDL1, CD8, PD-1 and FOXP3). These initial proteins have been selected because they are targets for existing immunotherapies and there are publications supporting their use as predictors of response. ImmunoProfile will work with its Steering Committee to monitor

the relevance of different proteins and to select new immuno-regulatory proteins to add to the test.

Before October 2022, ImmunoProfile was performed in a clinical laboratory that was certified by CLIA, under CLIA guidelines for clinical testing. After October 2022, ImmunoProfile is performed in a clinical laboratory no longer certified by CLIA; however, the staining procedures and quantification methodology remain unchanged. The study results will not be released to subjects or into patient electronic medical records.

Study-Specific Biomarker Selection and Cohort Allocation
Subjects whose tumors are PD-L1 positive and/or CD8+ T cell inflamed using ImmunoProfile without the presence of DDRD will be assigned to Cohort 2.

PD-L1 positivity will be defined as Combined Positive Score (CPS) ≥ 1, which is the number of PD-L1 staining cells (e.g., tumor cells, immune cells) divided by the total number of tumor cells, multiplied by 100. CD8+ T cell inflammation will be defined as CD8+ T cell density ≥ 200, which is the number of CD8+ cells divided by the surface area of a region of interest (mm^2).

Subjects whose tumors do not harbor DDRD and are PD-L1 negative with low CD8+ T cell infiltration will be assigned to Cohort 3. Subjects whose prescreening is unsuccessful for cohort allocation or whose biomarker status matches that of a filled cohort will not be eligible.

9.2 Correlative Studies

Correlative studies in this trial will be exploratory in nature. The immunomodulatory properties of nivolumab in combination with docetaxel and ADT will be explored and correlated with clinical outcomes. In addition, the ability of tissue-level biomarkers to predict clinical outcomes after chemohormonal-immunotherapy will be examined. Because the study prospectively enriches for mHSPC patients harboring DDRD (Cohort 1), the immunogenicity of different types of DDRD will be evaluated. For the subset of subjects who undergo metastatic biopsies for clinical purposes (see Section 9.2.3), the genomic and transcriptomic profiles from metastatic biopsies will be compared to that of their primary prostate biopsy. Finally, leveraging information collected during pre-screening, we will examine the genomic and immune landscape of de novo mHSPC as well as their prognostic value in clinical outcomes for mHSPC, independent to treatments received.

9.2.1 Peripheral Blood Mononuclear Cells (PBMCs), Chemokines, Cytokines, and cfDNA

Blood will be collected at timepoints specified in Section 10 for PBMC analysis by flow cytometry and chemokines and cytokines analysis by Luminex. Plasma from this collection will also be banked for cell-free DNA (cfDNA) analysis. If the total volume of blood is unable to be collected at each timepoint, assays will be prioritized appropriately, and the event will not be considered a violation. The DFCI Immune Assessment Laboratory of Center for Immuno-Oncology will perform these correlative studies.

9.2.2 **Circulating Tumor Cells (CTCs)**

Blood will be collected at timepoints indicated in Section 10 for CTC analysis including CTC quantification and PD-L1 and MHC class I expression analysis. If the total volume of blood is unable to be collected at each timepoint, assays will be prioritized appropriately, and the event will not be considered a violation. The Lang Laboratory at the University of Wisconsin will perform these correlative studies.

9.2.3 **Tissue Studies**

Adequate baseline FFPE tissue from either (1) prostate biopsy, (2) TURP tissue, or (3) metastatic biopsy tissue (excluding tissue from bone and lymph node biopsies) is mandatory for integral biomarker analysis (OncoPanel and ImmunoProfile; See Sections 3.1 and 9.1). If archival FFPE tissue is unavailable or insufficient for OncoPanel and ImmunoProfile analysis, subjects must be undergoing a standard of care biopsy for clinical purposes that will provide material meeting the requirements for these assays in order to be eligible. Archival FFPE tissue will be requested for additional exploratory correlative studies when available but is not mandatory. Subjects who undergo a baseline or on-study metastatic biopsy for clinical purposes will have paired analysis of the primary and metastatic biopsy tissues. Tissue-level analysis will be conducted to examine mechanisms of response and resistance and includes genomic and transcriptomic profiling by whole exome and RNA sequencing.

10. STUDY CALENDAR

Main study baseline evaluations are to be conducted within 4 weeks prior to start of study treatment chemoimmunotherapy. Imaging scans must be done ≤ 4 weeks prior to the start of study treatment chemoimmunotherapy. In the event that the subject's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any chemoimmunotherapy study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Follow-up data will be collected per section 5.6.

Table 8. Study Calendar

	Screening[15]		**Treatment**		**End of treatment**	**Follow-up**
	Pre-screening	Main study (Day -28 to -1)	Cycles 1-6 (Every 3 weeks) ± 3 days	Cycles 7-28 (Every 4 weeks) ± 3 days	Within 6 weeks after last dose of nivolumab	Every 12 weeks after EOT ± 14 days
Administrative Procedures						
Pre-screening informed consent[1]	X					
Main study informed consent		X				

Review of eligibility criteria		X				
Demographics		X				
Medical history		X				
Concomitant medications		X	X	X	X	
Nivolumab administration[2]			X	X		
Docetaxel administration[2]			X			
Abiraterone Acetate (optional)				X[16]		
LHRH analogue administration[2]	X					
Post-study anticancer therapy					X	X
Survival status[3]						X
Clinical Procedures and Assessments						
Adverse event evaluation			X	X	X	X
Vital signs and Physical exam[4]		X	X	X	X	X
Height		X				
Weight		X	X	X	X	
ECOG performance status		X	X	X	X	X
Laboratory Procedures and Assessments						
CBC with differential[5]		X	X	X	X	
Chemistry (CMP)[6,16]		X	X	X	X	
Coagulation (PT/INR, aPTT)		X				
TSH[7]		X	X	X	X	
HBV/HCV[8]	X					
LDH[9]		X	X	X	X	
Urinalysis[10]		X				
Testosterone[11]	X	X	X	X	X	X
Efficacy Measurements						
PSA[11]	X	X	X	X	X	X
Tumor imaging[12]		X		X (Wk 30, 52, 104)		
Archival Tissue Collection, Tumor Biopsies, and Correlative Studies						
Archival Tissue Collection[13]	X					
Fresh Tissue Biopsy[13]	(X)					
Research blood collection[14]	(X)		X (C1 and C2)	X (C10 and C15)		

1. Pre-screening consent for assessment of (1) DNA repair defect(s) by OncoPanel and (2) CD8 and PD-L1 staining by ImmunoProfile in tumor tissue is required for cohort allocation. Patients will be assigned to the following cohorts (N=20 per cohort), if pre-screening is successful for cohort allocation, main study eligibility criteria met, and the respective cohort has not been filled.
    a. Cohort 1: Subjects whose tumors harbor somatic or germline homozygous deletions and/or deleterious mutations in a DDR gene using OncoPanel, or are MMR-d or MSI-H, regardless of ImmunoProfile results.
    b. Cohort 2: Subjects whose tumors are PD-L1 positive and/or CD8+ T cell inflamed using

ImmunoProfile without presence of DDRD.

c. Cohort 3: Subjects whose tumors do not harbor DDRD and are PD-L1 negative with low CD8+ T cell infiltration

2. See Section 5.1 for details on nivolumab, docetaxel, and LHRH analogue treatment regimens.
3. All subjects, including those who discontinue chemotherapy and/or immunotherapy early, will be followed until radiographic progression (PCWG3 criteria) assessed by treating physician, or death, withdrawal of consent, or study termination, whichever occurs first. After radiographic progression, subjects will be followed for overall survival annually via chart review and/or telephone call until study termination. Subjects removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE (See Section 5.6). Patients who underwent pre-screening (OncoPanel and ImmunoProfile) but were not enrolled onto the study may have their medical records reviewed retrospectively to provide data for exploratory objectives.
4. Vitals signs include blood pressure (BP), heart rate (HR), respiratory rate (RR), O2 saturation, and temperature. Full physical examination at baseline. Targeted physical examination at other time points.
5. Basophils (BASOP), eosinophils (EOSP), hematocrit (HCT), hemoglobin (HGB), lymphocytes (LYMP), monocytes (MONP), neutrophils (NEUTP), platelet count (UNVPLT), red blood cell count (RBC), total white blood cell count (WBC)
6. Albumin (ALB), alkaline phosphatase (ALK), total bilirubin (TBILI), bicarbonate (CO2), blood urea nitrogen (BUN, or urea depending on local practice), calcium (CA), chloride (CL), creatinine (CREAT), glucose (GLU), potassium (K), total protein (TP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (NA).
7. Free T3 and free T4 will only be collected if TSH is abnormal, or if there is clinical suspicion of an AE related to the endocrine system.
8. Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, antibodies against hepatitis B core antigen), and HCV serology (anti- HCV) will be performed. HBV DNA test is required for subjects who have known positive serology for anti HBc. HCV RNA test is required for subjects who have known positive serology for anti HCV.
9. Lactate dehydrogenase
10. Urinalysis: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, color and appearance. Microscopy should be used as appropriate to investigate WBCs and use the high-power field for RBCs.
11. Subjects will check PSA at time of ADT initiation (or as close as possible if ADT commences prior to consent), time of pre-screening, main study screening, every 3 weeks (± 1 week) during weeks 1-18, then every 4 weeks (± 1 week) after week 18. Testosterone will be checked every 6 weeks (± 1 week) during weeks 1-18, then every 8 weeks (± 1 week) after week 18.. Weeks are in reference to calendar week and should not be adjusted for dosing delays. Every effort should be made to have PSA checked in the same laboratory.
12. Radiographic evaluations and tumor measurements will be performed at Screening, Week 30 (to correlate with 7-month PSA timepoint), Week 52 (to correlate with 12-month PSA timepoint), and Week 104 ± 1 week. Weeks are in reference to calendar week and should not be adjusted for dosing delays. CT chest/abdomen/pelvis with contrast and bone scan should be performed. MRI abdomen and/or pelvis may be used in place of CT if deemed clinically necessary; however, the same imaging modalities should be used throughout the study. ** Scans performed prior to consent will be allowed for screening and confirmation of eligibility if performed within 12 weeks prior to day 1 start of study treatment.
13. Adequate FFPE tumor tissue is required for OncoPanel and ImmunoProfile biomarker analysis. If archival tissue is unavailable or insufficient, subjects must be undergoing a standard of care biopsy that will provide material meeting the above requirements in order to be eligible. If available, additional archival FFPE tissue will be requested for correlative studies. See Section 3.1 for details.
14. Blood will be collected at room temperature for correlate studies (see Sections 9.2.1 and 9.2.2) at the following timepoints: during pre-screening (optional) and before treatment infusions during Cycles 1, 2, 10, and 15 (mandatory). If the total volume of blood is unable to be collected at each timepoint, assays will be prioritized

appropriately, and the event will not be considered a violation.

15. Before one of the study cohorts enrolls 15 of 20 patients (Cohort 3 is anticipated to complete accrual first), subjects may undergo main study screening when ImmunoProfile and OncoPanel analyses are ongoing, and may proceed to C1D1 treatment if they meet all eligibility criteria with the exception that OncoPanel analysis is ongoing. These patients will be allocated into their respective cohort after OncoPanel results return.
16. Patients who meet the 7-month primary objective and have completed chemoimmunotherapy will have the option to begin on abiraterone acetate by physicians discretion. For participants who choose to start abiraterone and prednisone, AST and ALT will be checked every two weeks for at least first two months. Participants are permitted to have LFT checks locally.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, subjects should be re-evaluated for radiographic response during Week 30, Week 52, and Week 104 ± 1 week. Weeks are in reference to calendar week and should not be adjusted for dosing delays. CT chest/abdomen/pelvis with contrast and bone scan will be performed.

Measurable lesions are not required for study eligibility. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009) with noted caveats for measurable disease adopted in the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG3) (Scher 2016).

11.1.1 Definitions

Evaluable for Target Disease response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable disease in visceral organs is defined as at least 1 lesion > 10 mm in its longest diameter as measured with CT scan. Lymph node disease is considered measurable if the baseline node measures ≥ 1.5 cm in short dimension. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters (or decimal fractions of centimeters). Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast

disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

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

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

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

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

11.1.3 Methods for Evaluation of Disease

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

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as

assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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 data 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 from CT, MRI may be used instead of CT in selected instances.

11.1.4 **Response Criteria**

11.1.4.1 **Evaluation of Target Lesions**

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.4.3 Evaluation of New Lesions

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

11.1.4.4 Evaluation of Best Overall Response

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

Table 9. Evaluation of Best Overall Response for Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.			

Table 10. Evaluation of Best Overall Response for Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 **Time to Event Assessments**

Overall Survival: Overall Survival (OS) is defined as the time from start of chemoimmunotherapy to death due to any cause or censored at date last known alive.

Time to Castration Resistance: Time to castration resistant disease is defined as the time from start of chemoimmunotherapy to date of documented clinical or serological progression with castrate-level testosterone level (<50 ng/dL), it is censored at the date of last disease assessment for those without the events.

Time to Clinical Progression: Time to clinical progression is defined as the time from start of chemoimmunotherapy to date of documented clinical progression, defined by increasing symptomatic bony metastasis per PCWG3 criteria, non-bone progression per RECIST 1.1 criteria, or clinical deterioration due to cancer based on investigator's judgment, or it is censored at the date of last disease assessment for those without progression.

Time to PSA or Serologic Progression: Time to PSA or serologic progression is defined as the time from start of chemoimmunotherapy to the date of documented at least ≥50% increase in serum PSA (with the lowest PSA level (nadir) as reference), or it is censored at last PSA test date for those who did not have PSA progression.

- Two consecutive PSA increases must be documented with each measurement obtained at least 2 weeks apart.
- The date of the first recorded increase will be the date of progression.
- In subjects who achieve a PSA nadir less than 4ng/mL, serologic progression will require a confirmatory increase with PSA above 4 ng/mL.
- The unconfirmed increase may be a PSA value less than 4 ng/mL but must be at least 50% increase above the PSA nadir.

11.2 Other Response Parameters

PSA nadir ≤0.2 ng/mL at 7 months was recently shown to be prognostic for overall survival in mHSPC patients treated with ADT alone or ADT plus upfront docetaxel in the phase 3 E3805 CHAARTED trial (Harshman 2018). In this study, the proportion of patients achieving PSA nadir ≤0.2 ng/mL at 7 months will be assessed.

12. DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Data Collection and Management

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

12.1.1 Electronic Case Report Forms (eCRFs)

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

12.1.2 **Source documents**

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

12.1.3 **Record retention**

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

12.2 Study Monitoring and Quality Assurance

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research.

Information that raises any questions about subject safety will be addressed with the Sponsor-Investigator and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date subject accrual; current dose level information; DLT information; all Grade 2 or higher unexpected AEs that have been reported; summary of all deaths occurring within 30 days of intervention for Phase 1 or Phase 2 protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g., scans, laboratory values) will be provided upon request.

In addition to review by DSMC, the PCCTC will conduct regularly scheduled monitoring visits.

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

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

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

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

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

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

12.3 Data Reviews and Queries

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

12.4 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, the PCCTC Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The PCCTC is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and AE reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the PCCTC.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open-label, multicohort, phase 2 study of nivolumab in combination with docetaxel and ADT in patients with newly diagnosed (de novo) mHSPC. Patients whose tumor harbors

DDRD(s) or an inflamed tumor microenvironment by CD8 or PD-L1 staining will be prospectively enriched using the OncoPanel and ImmunoProfile assays, respectively. Three biomarker cohorts will be enrolled: Cohort 1 includes patients with DDRD with or without inflamed tumors, Cohort 2 includes patients with inflamed tumors without DDRD, and Cohort 3 includes patients with biomarker negative tumors. All patients will receive continuous ADT (LHRH analogue,), docetaxel 75 mg/m^2 plus nivolumab 360 mg IV Q3W for 6 cycles, followed by nivolumab 480 mg IV Q4W for up to 2 years in total duration. The primary endpoint is proportion of patients with PSA ≤ 0.2 ng/mL at 7 months from start of chemoimmunotherapy. Month is defined as approximately 30 days, which is aligned with the Cycle-10 PSA measurement and the 30-week radiographic evaluation timepoint. Patients have the option of starting SOC abiraterone acetate with prednisone at the discretion of the treating physician after completing planned docetaxel chemotherapy and the 7-month primary endpoint is reached.

13.2 Sample Size, Accrual Rate and Study Duration

From the phase 3 E3805 CHAARTED study, 397 patients were treated with ADT plus docetaxel, and 214 (54%) of whom had high-volume disease and no prior local therapy (de novo presentation). Of these, the rate of PSA ≤0.2 ng/mL was 28% at 7 months and 19% at 12 months from ADT initiation (unpublished data from E3805 investigators). Given that patients may have started ADT up to 140 days prior to initiation of chemoimmunotherapy (section 3.2.1), we assume that a rate of 20% of patients with PSA ≤ 0.2 ng/mL at 7-months of chemoimmunotherapy is not acceptable and a true rate of 45% or higher will be considered promising for this chemohormonal-immunotherapy combination in patients with de novo mHSPC.

The study plans to enroll 20 patients in each cohort, with a total sample size of 60 patients. Based on a one-sample exact binominal test, if 7 or more of 20 patients have PSA ≤ 0.2 ng/mL at 7 months (observed rate of 35%), we will conclude that the combination treatment warrants further study in the respective cohort. The probability of concluding that treatment is effective is 0.87 (statistical power) if the true rate of PSA ≤ 0.2 ng/mL at 7 months is 45% or higher. The probability of concluding that the treatment is effective is 0.09 (i.e. one-sided type I error) if the true rate is 20% or less.

Assuming 30% positive biomarker screening rate (DDRD and/or inflamed tumor), approximately 130 patients will be screened to enroll 40 patients into Cohort 1 and 2. Based on the frequency of biomarker positivity (approximately 15% for DDRD and 30% for inflamed tumor), we anticipate Cohort 3 to complete accrual before Cohort 2, followed by Cohort 1. We expect to complete study accrual in a total of 36 months, at a rate of 1-2 subjects per month. All subjects will be followed for 2 years after the last dose of study immunotherapy, death, or study termination, whichever occurs first. The total study duration is anticipated to be 5 years.

13.3 Interim Monitoring Plan

The combination of PD-1/PD-L1 axis inhibition and cytotoxic chemotherapy has been shown to be safe and clinically active for patients with various advanced malignancies, including NSCLC, SCLC, and TNBC (See Section 2.5.2). Phase 3 studies across these varying histologies

demonstrated that PD-1/PD-L1 inhibitor plus chemotherapy had safety profiles consistent with known AEs of each agent, with no new AE signals observed. We anticipate the chemohormonal-immunotherapy combination investigated in this study will be tolerable in a treatment-naïve population of mHSPC patients; therefore, no interim safety analysis is planned.

13.4 Analysis of Primary Endpoint

The proportion of patients with PSA ≤ 0.2 ng/mL at 7-months ± 2 weeks from start of chemoimmunotherapy will be summarized with 80% two-sided exact binominal confidence interval (CI). For patients without interruptions in study treatment, the 7-month timepoint is aligned with the cycle-10 PSA measurement (estimated at week 31±1 week per study calendar). Patients who are off study without PSA measure at 7 months will be conservatively counted as non-PSA response. The primary analysis will be conducted separately by each cohort. A pooled analysis of all cohorts 1-3 will not be performed as these cohorts are biomarker-selected, not representing the overall population in patients with newly diagnosed mHSPC.

13.5 Analysis of Secondary Endpoints

The rate of PSA ≤ 0.2 ng/mL after receiving at least one dose of study treatment (docetaxel and nivolumab) and before initiation of other systemic therapies (including protocol-allowed abiraterone after month 7) and objective response rate (per RECIST 1.1 criteria) in subjects with measurable disease will be summarized with 95% two-sided exact binomial CI by each cohort.

Time to event endpoints (overall survival, time to castration resistant disease, time to clinical progression, and time to PSA or serologic progression, as defined in Section 11.1.5) will be estimated using the Kaplan-Meier methodology by biomarker cohort. For PSA- and image-based time-to-event endpoints, if patients start abiraterone acetate prior to occurrence of the corresponding events, the endpoint will be censored at last disease evaluation prior to initiation of abiraterone initiation. From the CHAARTED study, the median time to castration resistant disease was 20 months, and the median time to clinical progression was 30 months in patients who received the combination of ADT and docetaxel. From the adjuvant PD-1 phase III studies in other GU cancers (KEYNOTE-564, CheckMate 274), approximately 20~25% of patients discontinued PD-1 treatment due to adverse events and these patients would be more likely to switch treatment. Therefore, if we observe a large proportion of patients (defined as ≥30% of subjects within 2 years of chemoimmunotherapy) switch to abiraterone acetate without progression, we will conservatively only report the 7-month event-free rate along with 95% CI.

For toxicity reporting, all AEs will be graded and analyzed using CTCAE v5.0. Type of AEs, intensity (grading), and attribution will be provided in a listing. The worst grade will be used if any toxicity event is reported multiple times on the same subject. All AEs resulting in discontinuation, dose modification, and/or dosing interruption, and/or treatment delay of drug will also be summarized. All laboratory test results will be classified according to the CTCAE version 5.0.

13.6 Analysis of Exploratory Endpoints

OncoPanel and ImmunoProfile biomarker analysis (as described in section 9.1) using baseline tumor tissue will be performed for allocation of patients into a study cohort during pre-screening. The 95% two-sided exact binominal CIs will be provided to estimate the prevalence of DDRD and/or inflamed tumors in the screening population.

Genomic and transcriptomic profiling will be analyzed via whole exome sequencing (WES) and RNA sequencing (RNA-seq) in baseline biopsy tissues. To detect a rare type of mutation, there are 0.94 and 0.70 probabilities to observe ≥3 mutations if the true underlying mutation rate is 5% and 3%, respectively, assuming 120 (~90%) of screening patients with successful biomarker analysis.

Clinical outcomes will be summarized in subgroups defined by the individual and joint utility of PD-L1 staining, CD8 staining, DDR status, tumor mutation burden (TMB), genomic alterations, and transcriptomic signatures. For example, assuming 30% PD-L1+ for Cohort 1 and 60% PD-L1+ for Cohort 2 (with a total of 18 PD-L1+ tumors), the 95% exact binomial CI for PSA or objective response rate will not be wider than 0.48 in the group with PD-L1+ tumors.

For subjects with DDR defects enrolled in cohort 1, ImmunoProfile results and immune signatures by RNA-seq will be assessed by different types of DDRD (e.g., MMR vs. homologous recombination repair; monoallelic vs. biallelic alterations). The types of DDRD will be correlated with clinical outcomes as exploratory analyses. Furthermore, DDRD functional assays—including Rad51 staining for homologous recombination (HR) genomic alterations—will be carried out, and these results will be correlated with immune contexture and clinical outcomes.

For the subset of subjects with paired primary and metastatic biopsy tissues, genomic and transcriptomic profiling will be conducted in the paired biopsies to evaluate tumor heterogeneity and evolution.

To compare pre-post therapy values in any quantitative blood-based biomarkers, including PBMCs, cytokines, chemokines and CTCs, there is 80% power to detect an effect size of 0.63 within a cohort (n=20), using a paired t-test (two-sided α=0.05). Two-sample t-test or Wilcoxon rank sum test will be conducted to compare quantitative biomarkers between PSA responders (PSA ≤ 0.2 ng/mL at 7 months) and non-responders as exploratory analysis.

Finally, for patients consented for follow-up during pre-screening regardless of study enrollment, baseline genomic aberrations and immune infiltration determined by OncoPanel and ImmunoProfile assays will be correlated with clinical outcomes, including time to castration resistance and overall survival. Findings will be reported in a descriptive manner.

13.7 Reporting and Exclusions

The following Analysis Populations are planned for this study:

Safety Analysis Set: Evaluation of toxicity will be done in the safety population, which will include all subjects who received at least one dose of docetaxel and nivolumab.

Full Analysis Set (FAS): The FAS will include all subjects who are deemed eligible in each cohort and receive at least one dose of study chemoimmunotherapy (docetaxel and nivolumab). FAS will be used for all efficacy endpoints. Subjects who are off study prior to 7 months or early death from any causes will be included in the main analysis of rate of PSA $\leq$ 0.2 ng/mL at 7 months as non-responders.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B MULTI-CENTER GUIDELINES

DFCI IRB Protocol #: [19-384]

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

1. INTRODUCTION

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

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution (DFCI) is working with the PCCTC as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor-Investigator: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

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

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc.) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). The Lead

Institution (DFCI) is working with the PCCTC as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible for ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data. The database for this trial will be managed by the PCCTC.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, **Xiao X. Wei, MD** will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling subjects) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials), as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and provide information for DF/HCC to register subjects from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of subjects to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling subjects and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register subjects through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.

- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening causes: Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

Protocol closures and temporary holds: Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

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

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

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

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

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

The Coordinating Center will not register subjects if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study subject must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the subject in the trial, rather than limited data sets with data use agreements.

3.7 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the subject are strictly confidential. Whenever reasonably feasible, any subject specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be

used for all subject specific documents. Subject initials may be included or retained for cross verification of identification.

3.8 DF/HCC Multi-Center Protocol Registration Policy

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

Subject Registration and Randomization

To register a subject, the following documents should be completed by the Participating Institution and e-mailed to PCCTC Project Manager:

- Copy of all source documents required to verify eligibility
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Provide information for DF/HCC to register the subject on the study with the DF/HCC Clinical Trial Management System (CTMS).
- The Coordinating Center will inform the Participating Institution and provide the study specific subject case number, and, if applicable, assigned treatment and/or dose level.

Treatment or other protocol-specific interventions may not begin without confirmation from the Coordinating Center that the subject has been registered.

Initiation of Therapy

Participating Institutions must receive eligibility confirmation from the Coordinating Center before the initiation of treatment or other protocol-specific interventions. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

Eligibility Exceptions

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

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

Protocol Deviations, Exceptions and Violations

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

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

Definitions
Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g., enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

Reporting Procedures
DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

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

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the participating institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study subjects. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study subjects.

All subjects receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by subjects. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

Guidelines for Reporting Serious Adverse Events
Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy/IRB of record's Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

Guidelines for Processing IND Safety Reports
The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to the IRB according to their institutional policies and procedures.

3.10 Data Collection and Management
Standardized eCRFs and CRF Completion Guidelines will be created by the PCCTC for the collection of study data. Access and training for PCCTC Medidata Rave EDC will be made available to participating sites upon local regulatory approval.

Data entry should be done with 14 calendar days from being collected. Queries should be answered (response entered into the EDC within 14 calendar days of being issued.

See Section 12 of the main protocol for additional information.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8 and in additional supplemental ordering information.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance
The Participating Institutions may be required to submit subject source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality,

and subject safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in periodic Coordinating Center initiated teleconferences. Teleconferences may include highlighting overall protocol progress and other important announcements.

5.2 Monitoring Reports

The DF/HCC Sponsor will have access to all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor or the Coordinating Center may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Participating institutions should aim for a minimum target of four patients per site annually. Sites that are not meeting their accrual expectations may be subject to termination.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

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

6.2 Audit Notifications

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

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per

DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

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

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The subject _____ is enrolled on a clinical trial using the experimental agents **docetaxel and nivolumab**. Patients also have the option of starting standard of care **abiraterone acetate** after completing combination chemotherapy plus immunotherapy. This clinical trial is sponsored by Dana-Farber Cancer Institute. This form is addressed to the subject, but includes important information for others who care for this subject.

Docetaxel and abiraterone acetate interact with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Docetaxel and abiraterone acetate interact with a certain specific enzyme(s) in your liver.

- The enzyme in question is ***CYP3A4***, and docetaxel and abiraterone are broken down by this enzyme in order to be cleared from your system (i.e. substrates).
- Abiraterone also inhibits another enzyme in your liver: ***CYP2D6*** which breaks down certain medications for clearance from your system.
- Docetaxel and abiraterone must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start docetaxel or abiraterone, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of ***CYP3A4***".
- Before you start abiraterone, your study doctor will work with your regular prescriber to switch any medicines that are considered "CYP2D6 substrates with a narrow therapeutic index". If an alternative treatment cannot be used, your study doctor will consider dose a dose reduction of the concomitant CYP2D substrate.

- After completion of docetaxel chemotherapy (Cycle 1-6), CYP3A4 medications may be restarted at least 1 week after the last docetaxel administration. If a strong CYP3A4 inducer must be co-administered with abiraterone, your study doctor will consider increasing the abiraterone dose frequency.
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you drink grapefruit juice or eat grapefruit: Avoid these while you are receiving docetaxel chemotherapy.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are receiving docetaxel chemotherapy.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____ and he or she can be contacted at

_____

APPENDIX D MANAGEMENT ALGORITHMS FOR ORGAN-SPECIFIC AES FOR NIVOLUMAB (CTCAE 5.0)

These general guidelines constitute guidance to the Investigator.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

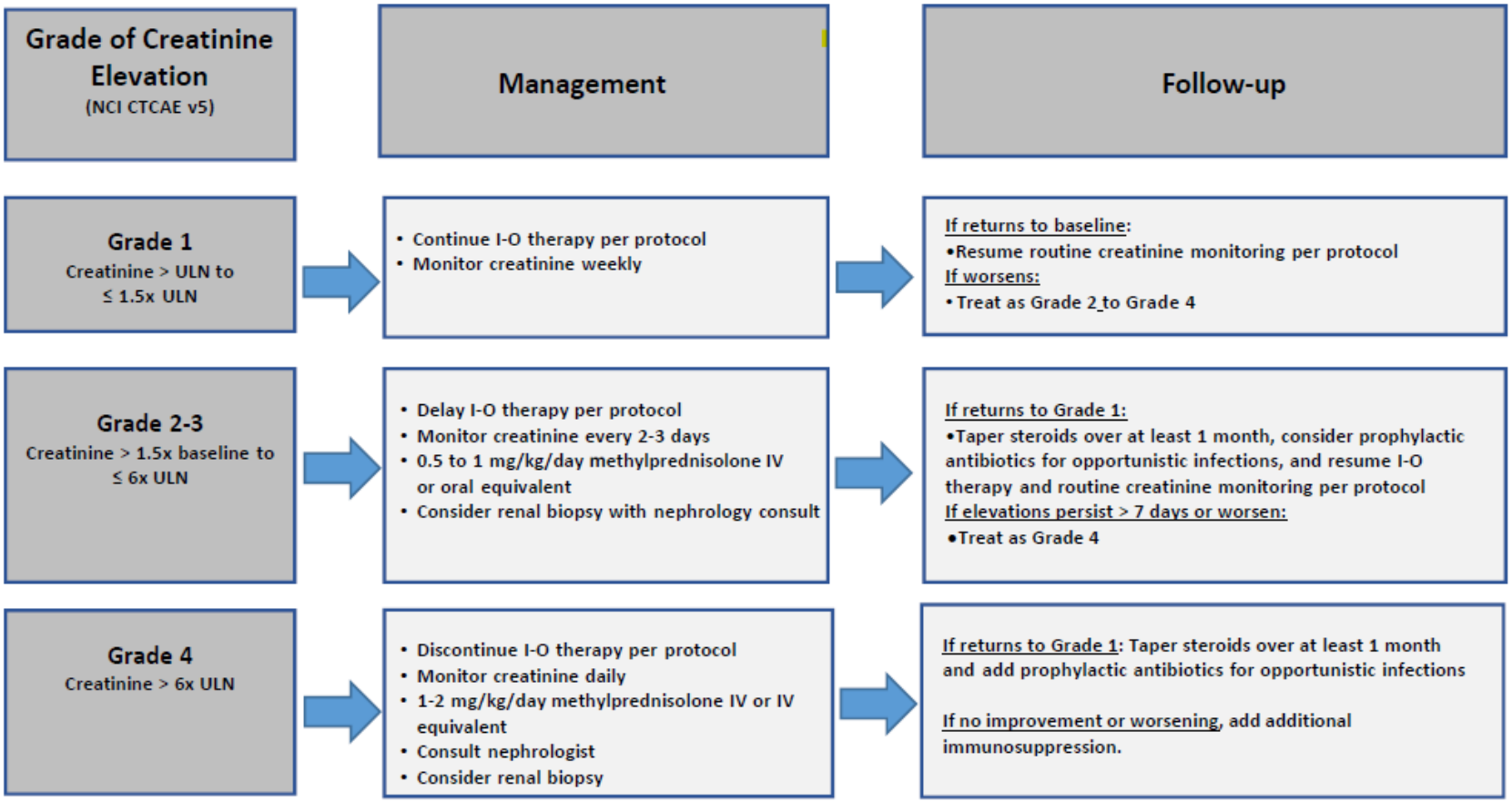
Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 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) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Renal Adverse Event Management Algorithm

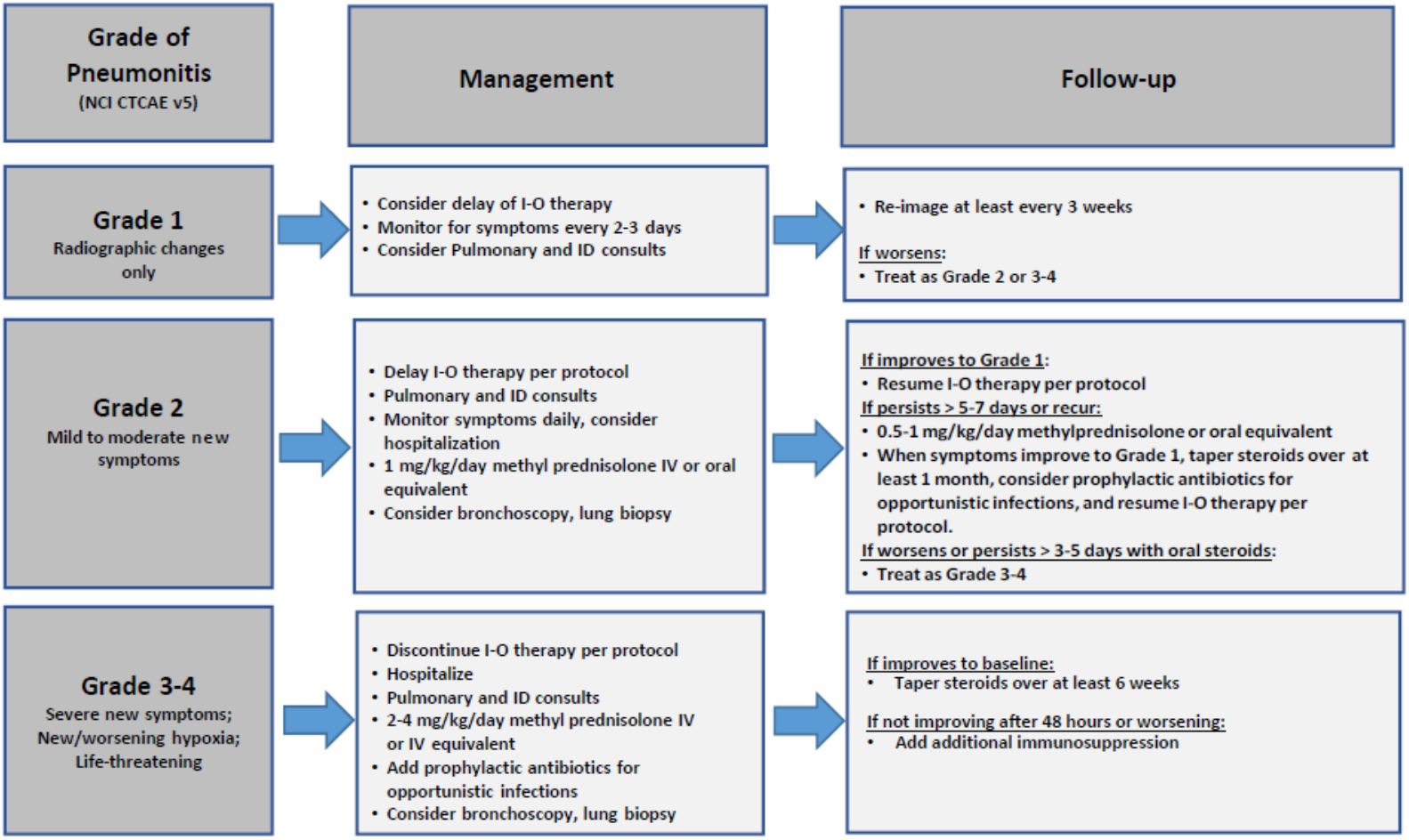
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

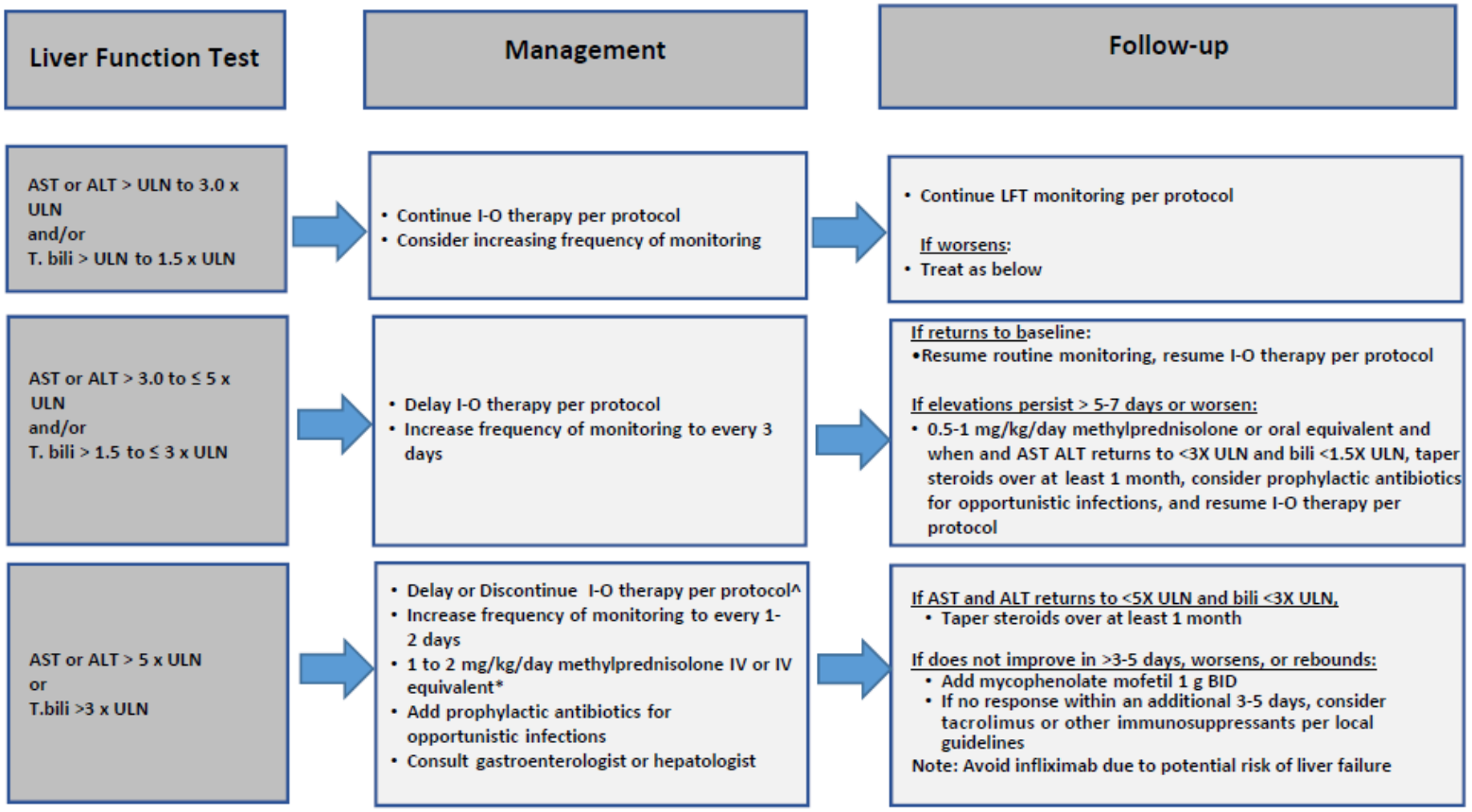
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

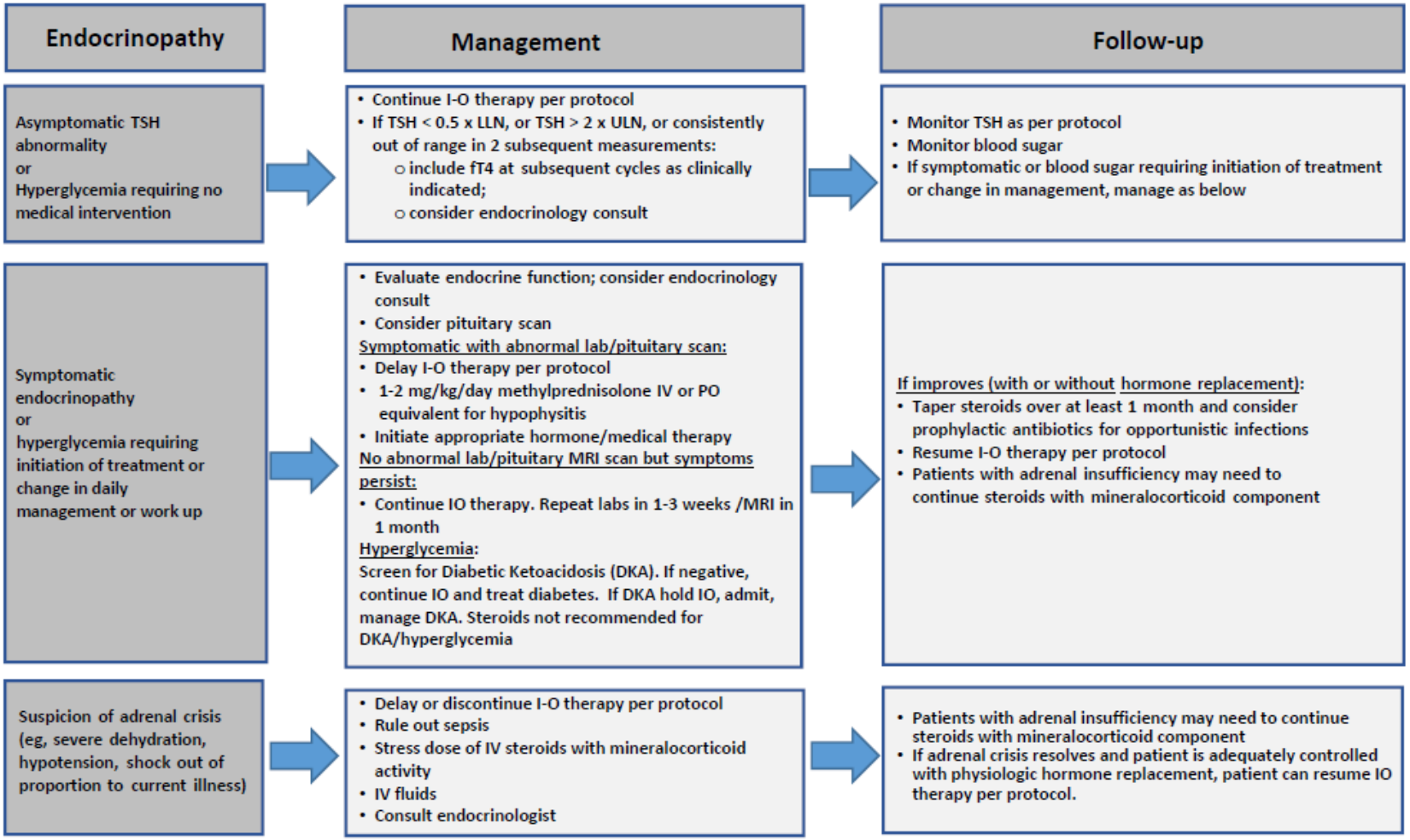
^ Please refer to protocol dose delay and discontinue criteria for specific details.

*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

For subjects with HCC, please refer to the protocol for specific details.

Endocrinopathy Adverse Event Management Algorithm

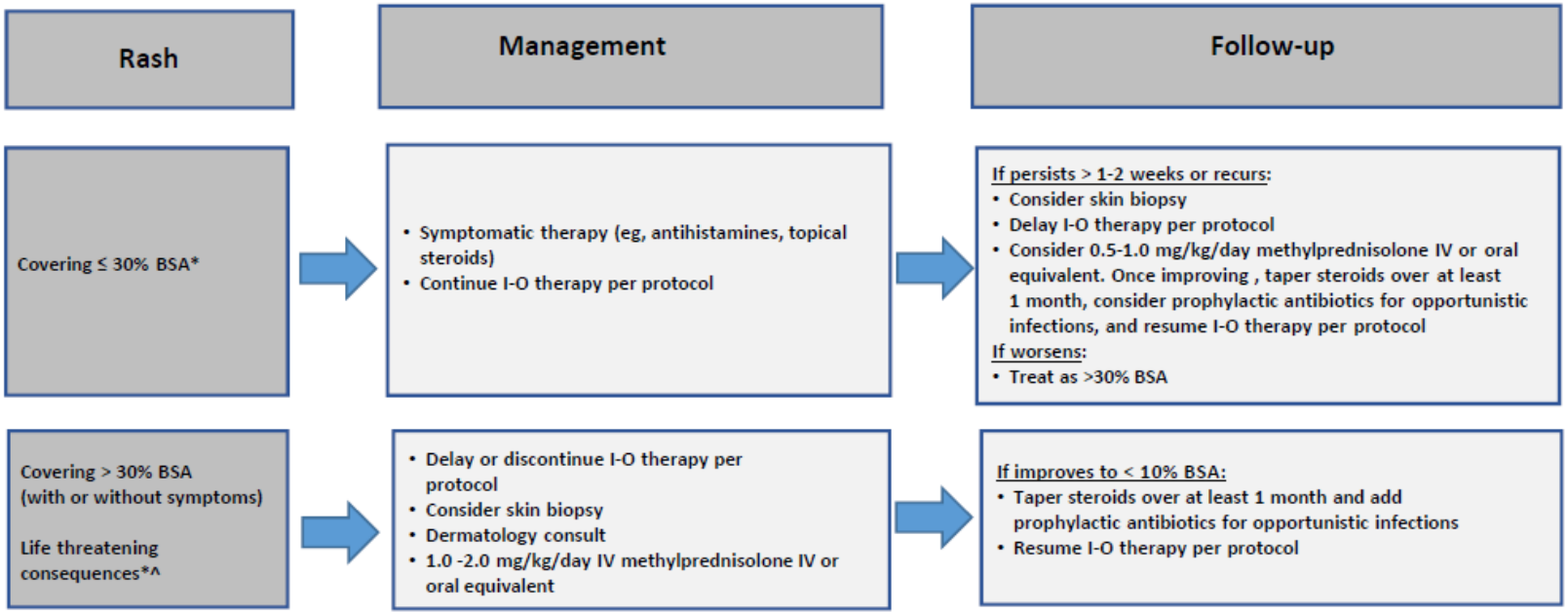
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

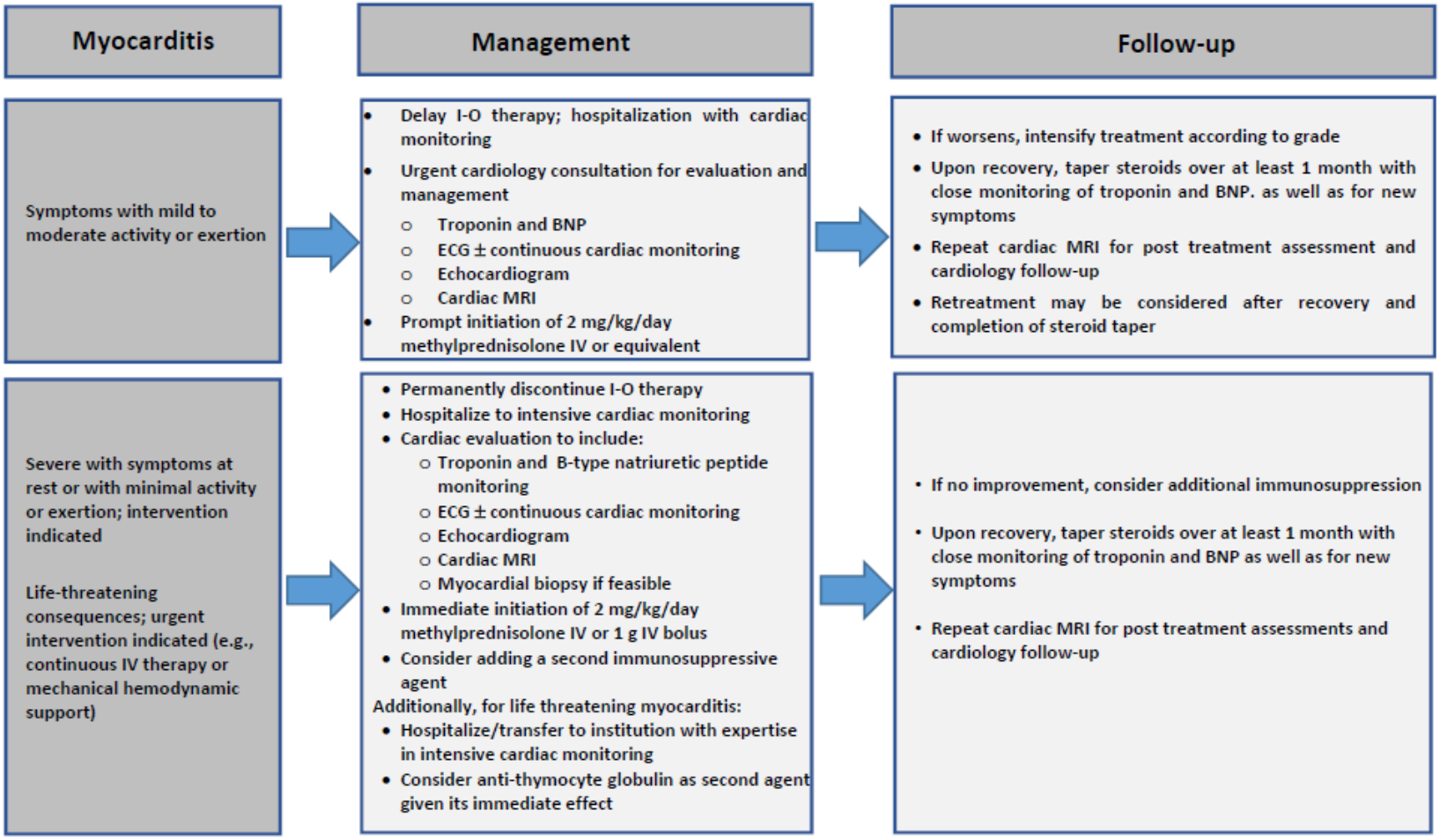
Grade of Neurological Toxicity (NCI CTCAE v5)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol • Discontinue I-O for select AEs^	• Continue to monitor per protocol. If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Discontinue I-O for select AEs^ • Consider neurology consult • Treat symptoms per local guidelines • Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent	If returns to baseline: • Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1-2 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.