NCT03007732

TITLE: Phase 2 Trial Pembrolizumab or Pembrolizumab in Combination with Intratumoral SD-101 Therapy in Patients with Hormone-Naïve Oligometastatic Prostate Cancer Receiving Stereotactic Body Radiation Therapy and Intermittent Androgen Deprivation Therapy

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).

2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.

3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.

4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.

I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

TRIAL SUMMARY

Abbreviated Abstract

Abbreviated Title	Pembrolizumab +/- SD-101 in Hormone-Sensitive Oligometastatic Prostate Ca with RT and iADT
Trial Phase	II
Clinical Indication	Patients with newly diagnosed, hormone-naïve oligometastatic prostate cancer who have not previously undergone radical prostatectomy or prostatic radiation
Trial Type	Open-label phase II study with safety lead-in
Type of control	Historical control
Route of administration	Pembrolizumab IV and SD-101 intraprostatic injection
Trial Blinding	None
Treatment Groups	Cohort 1 *(enrollment complete)* Arm 1: ADT + SBRT to ***prostate*** + Pembrolizumab Arm 2: ADT + SBRT to ***prostate*** + Pembrolizumab + ***SD-101*** Cohort 2 Arm 1: ADT + SBRT to ***prostate and oligometastatic sites*** + Pembrolizumab Arm 2: ADT + SBRT to ***prostate and oligometastatic sites*** + Pembrolizumab + ***SD-101***
Number of trial subjects	42 patients total
Estimated enrollment period	18 months
Estimated duration of trial	54 months
Duration of Participation	9 months on-treatment period

Full Abstract

Title	Phase 2 Trial of Pembrolizumab or Pembrolizumab in Combination with Intratumoral SD-101 in Patients with Newly Diagnosed Hormone-Naïve Oligometastatic Prostate Cancer Receiving Stereotactic Body Radiation Therapy and Intermittent Androgen Deprivation Therapy
Patient population	Patients with newly diagnosed, hormone-naïve oligometastatic prostate cancer who have not previously undergone radical prostatectomy or prostatic radiation.
Rationale for Study	Androgen deprivation therapy (ADT) is the mainstay of therapy for patients with hormone-sensitive metastatic prostate cancer. However, treatment is palliative, and the duration of response to ADT is variable before the development of castration resistant disease. Immune checkpoint antibodies that target the immune system have the potential to induce durable clinical responses in a subset of patients with different solid malignancies, including melanoma, NSCLC and RCC. However, immune checkpoint blockade in castrate-resistant prostate cancer (CRPC) that progressed after chemotherapy has not been very active (Kwon ED et al, 2014). Combination immunotherapy has the potential to activate multiple cellular components and augment anti-tumor immune responses (Larkin J et al, 2015). We hypothesize the combination of checkpoint blockade with the anti-PD-1 antibody pembrolizumab, and localized therapies that prime and augment an immune response, specifically definitive prostatic radiotherapy with or without intratumoral SD-101 (a TLR9 agonist), will induce a durable clinical response in a subset of patients with metastatic hormone-sensitive prostate cancer reflected by a prolonged period of PSA < nadir +2 ng/mL after cessation of all therapies including ADT.
Primary Objectives	<u>Cohort 1</u> 1. To assess the safety associated with giving RT and pembrolizumab with or without intratumoral SD-101. <u>Cohort 2</u> 1. To continue to assess the safety associated with giving RT and pembrolizumab with or without intratumoral SD-101. 2. To assess if the rate of PSA < nadir + 2 ng/mL at 15 months in patients with non-castrate levels of testosterone is greater than the historical control in each study arm.

Secondary Objectives	2. To determine the rate of testosterone-PSA uncoupling (section 3.2.3.1) in each study arm in cohort 2. Testosterone-PSA uncoupling is defined as PSA < 50% baseline and < 20ng/mL for at least 3 months after testosterone recovers to >150 ng/dL. In patients with metastatic hormone-sensitive prostate cancer off hormonal therapy, >90% patient are expected to have PSA increase to > 50% baseline after 3 months of testosterone recovery. 3. To estimate time to clinical progression in each study arm in cohort 2. 4. To estimate progression-free survival (PFS) in each study arm in cohort 2.
Exploratory Objectives	1. To assess peripheral and tumor-based biomarkers of response and resistance in both cohorts. 2. To define the treatment-induced effects on circulating immune cells in both cohorts. 3. To explore remodeling of circulating T cell repertoire in both cohorts. 4. To explore the concordance of PSMA-PET scanning with conventional imaging in oligometastatic prostate cancer patients in both cohorts.
Study Design	This is an open-label Phase 2 clinical trial combining stereotactic body radiation therapy (SBRT) and pembrolizumab with or without intratumoral SD-101 in patients with newly diagnosed hormone-naive oligometastatic prostate cancer. A safety lead-in for each treatment arm will be performed for the first 3 participants enrolled into each arm in cohort 1. For cohort 2, SBRT will be delivered to the whole prostate and all oligometastatic sites. Five (5) treatments will be delivered to the prostate and 3-5 treatments to oligometastatic sites every other day within a 10-21 day period. In both arms, marker placement and simulation will occur 1-5 weeks prior to start of pembrolizumab (C1D1). SBRT will start 1-5 weeks after marker placement and simulation. Subjects will start C1D1 and SBRT 1 month after ADT initiation at the earliest, and 4 months after ADT initiation at the latest. SD-101 will be injected into the dominant prostatic lesion at the time of fiducial marker placement, and 1-3 weeks after C1D1. SD-101 will be administered intratumorally in concert with prostate biopsies. Pembrolizumab will be continued for a total of 13 cycles, until disease progression, or unacceptable toxicity, whichever occurs first. Patients will receive 3 months of ADT run-in, followed by GnRH targeting agent (leuprolide preferred), abiraterone, and prednisone (or equivalent) for 9 months, then discontinuation of androgen deprivation therapy (ADT). Primary outcome is to evaluate the rate of PSA < nadir +2 ng/mL at 15 monthsfrom the start of treatment among patients with non-castrate levels of testosterone (>150 ng/dL). Serum, archival prostate biopsy, optional baseline metastatic tumor biopsy, and optional repeat biopsy at time of progression, will be obtained to characterize circulating and intratumoral immune responses.

Number of patients	Cohort 1: 10 participants Cohort 2: 32 participants Total: 42 participants
Duration of Therapy	Patients may continue treatment for 9 months (13 cycles) from the time of study entry.
Duration of Follow up	Patients will be followed every 12 weeks +/- 2 weeks for up to 3 years (years one and two are mandatory; year three is optional) after completion of therapy, until disease progression, removal from study, or death, whichever occurs first.
Duration of study	The study will reach completion 4.5 years from the time the study opens to accrual.
Study Drugs and Therapies	ADT: 3 month ADT run-in followed by leuprolide 22.5 mg every 3 months for 3 doses (or another FDA approved GnRH agent for 9 months) + abiraterone (e.g. Zytiga, Yonsa) with prednisone (or equivalent medication per local standard practice) for 9 months starting on Cycle 1 Day 1 (Arms 1 and 2). SD-101: 5 mg will be delivered to the dominant prostatic tumor lesion at time of fiducial marker placement (1-5 weeks prior to C1D1) and 1-3 weeks after C1D1, Arm 2 only. Pembrolizumab (Keytruda, MK-3475): 200 mg IV every 21 days for up to 13 doses (Arms 1 and 2). Radiotherapy: 7 Gy x 5 fractions (35 Gy total) delivered to the whole prostate gland and soft tissue oligometastases, 10 Gy x3 fractions (30 Gy total) to osseous metastases via stereotactic body radiation therapy (SBRT).

LIST OF ABBREVIATIONS

ABC	active-breathing control
ACE	angiotensin-converting enzyme
ADL	activities of daily living
ADT	androgen deprivation therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-KLM	liver kidney microsomal type 1 antibody
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BID	twice a day
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CBCT	Cone-beam CT
CD	cluster of differentiation
CFR	Code of federal regulation
CHR	Committee on Human Research (UCSF IRB)
CNS	central nervous system
CpG	cytidine-phospho-guanosine
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CRPC	castrate-resistant prostate cancer
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
CTV	clinical target volume
DFS	disease-free survival
DLT	dose limiting toxicity

LIST OF ABBREVIATIONS

DNA	Deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EPO	Erythropoietin
FDA	Food and Drug Administration
FFF	flattening-filter-free
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GNRH	gonadotropin-releasing hormone
GTV	gross tumor volume
Gy	Gray
HBeAg	hepatitis B “e” antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HER2	human epidermal growth factor receptor 2
HGB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HTN	hypertension
IB	Investigator’s brochure
IC	immune cells
ICF	Informed consent form
ICH	International Conference on Harmonization
ICRU	International Commission on Radiation Units and Measurements

LIST OF ABBREVIATIONS

IFN-α	interferon alpha
IgG4	immunoglobulin G4
IGRT	image guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity modulated radiation therapy
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
irAEs	immune-related adverse events
IRB	Institutional Review Board
irRC	immune-related response criteria
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
Na-F	sodium fluoride
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NSCLC	non-small cell lung cancer
ODN	Oligodeoxynucleotide
OHRP	Office for Human Research Protections
ORR	overall response rate
OTC	over the counter
PBMC	peripheral blood mononuclear cells
PCWG	Prostate Cancer Working Group
PD	disease progression
PD-1	programmed death 1 (PD-1)
pDC	plasmacytoid dendritic cells
PD-L1	programmed death-ligand 1 (PD-L1)
PD-L2	programmed death-ligand 2 (PD-L2)
PET	positron emission tomography

LIST OF ABBREVIATIONS

PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetics
PO	per os (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
PS	Phosphorothioate
PSA	prostate specific antigen
PSMA	prostate specific membrane antigen
PTT	partial thromboplastin time
PTV	planning target volume
PVC	polyvinyl chloride
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
QD	Once every day
RBC	red blood cell (count)
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	radiotherapy
SAE	Serious adverse event
SBRT	stereotactic body radiation therapy
SC	subcutaneous
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Order Classes
SOP	Standard operating procedure
t1/2	half-life
TCR	T cell receptor
TLR9	Toll-like receptor 9
TRUS	transrectal ultrasound
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

LIST OF ABBREVIATIONS

UTI	urinary tract infection
WBC	white blood cell (count)

TABLE OF CONTENTS

1.0 TRIAL DESIGN

1.1 Trial Design

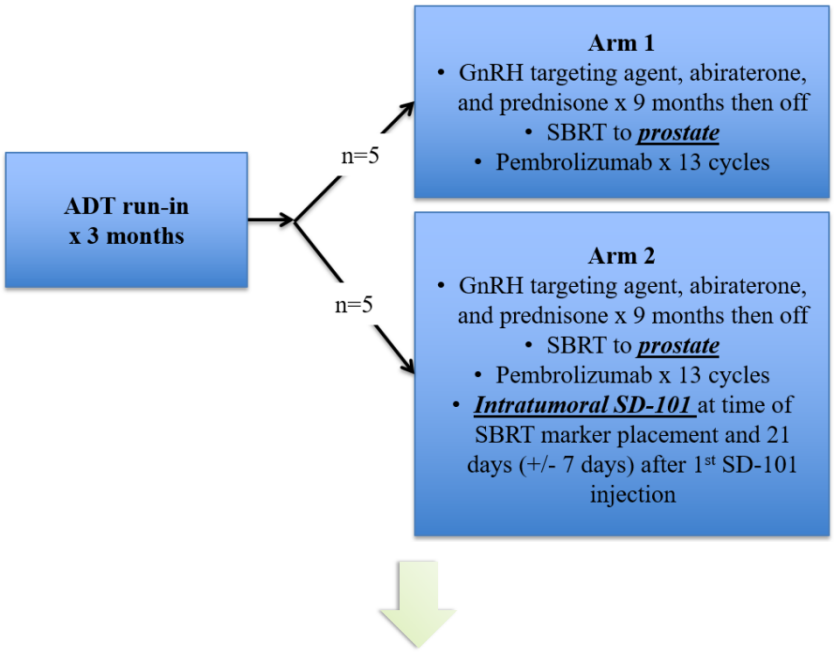
This is an open-label phase 2 clinical trial combining definitive prostatic radiotherapy (RT) and pembrolizumab with or without intratumoral SD-101 in patients with newly diagnosed hormone-naive oligometastatic prostate cancer.

A safety lead-in will be performed for the first 3 participants enrolled into each treatment arm in cohort 1. SBRT to the whole prostate ± oligometastatic sites will be administered 1-5 weeks after fiducial marker placement and SBRT simulation. 7 Gy x 5 fractions will be given via SBRT to the whole prostate and soft tissue oligometastatic sites (cohort 2 only) and 10 Gy x 3 fractions to osseous metastases (cohort 2 only), over 10-21 days. Fiducial marker placement and SBRT simulation will be performed 1-5 weeks prior to C1D1 (start of pembrolizumab). In Arm 2 (for both cohorts), SD-101 will be delivered to the dominant prostatic lesion at time of fiducial marker placement and 1-3 weeks after C1D1. Pembrolizumab will be continued for 13 cycles, until disease progression, or unacceptable toxicity, whichever occurs first. Patients will receive 3 months of ADT run-in, followed by GnRH targeting agent (leuprolide preferred), abiraterone, and prednisone (or equivalent) for 9 months, then discontinuation of androgen deprivation therapy (ADT). The primary outcome for cohort 2 is to evaluate the rate of PSA < nadir + 2 ng/mL after discontinuation of ADT 15 months from start of treatment among patients with non-castrate (>150 ng/dL) levels of testosterone. Serum, archival prostate biopsy, optional baseline metastatic tumor biopsy, and optional repeat biopsy at time of progression, will be obtained to characterize circulating and intratumoral immune responses.

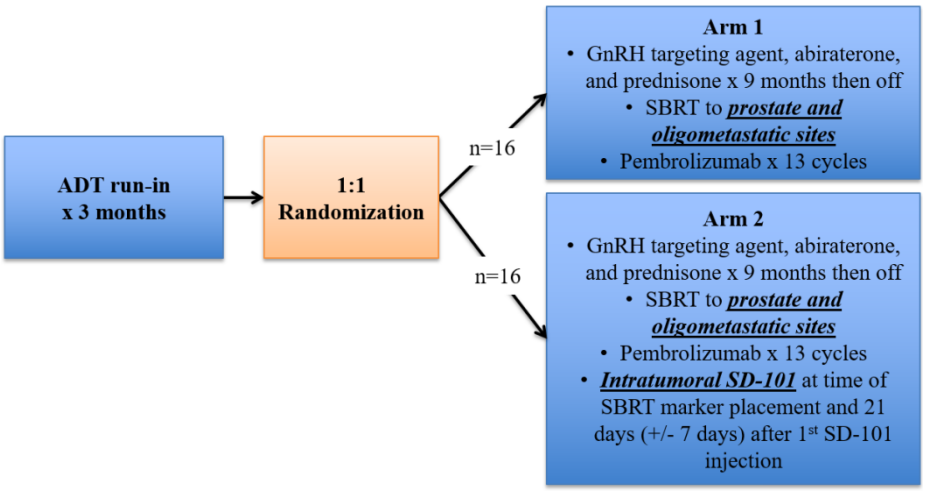
1.2 Trial Diagram

Cohort 1

[NOTE: As of 08/05/2019, cohort 1 completed enrollment and closed to accrual.]



Cohort 2



2.0 OBJECTIVE(S) & HYPOTHESIS(ES)

2.1 Primary Objective(s) & Hypothesis(es)

Cohort 1

(1) **Objective:** To assess the safety associated with giving RT and pembrolizumab with intratumoral SD-101.

Cohort 2

(1) **Objective:** To assess the safety associated with giving RT and pembrolizumab with or without intratumoral SD-101.

(2) **Objective:** To assess if the rate of PSA < nadir + 2 ng/mL at 15 months in patients with non-castrate levels of testosterone is greater than the historical control for each arm.

Hypothesis: The combination of PD-1 blockade with pembrolizumab and localized therapies that prime and augment an immune response—specifically SBRT with or without intratumoral SD-101, a TLR9 agonist—will induce a durable clinical response in a subset of patients with metastatic hormone-sensitive prostate cancer, reflected by a prolonged period of PSA < nadir + 2 ng/mL after cessation of all therapies including ADT. With standard of care intermittent ADT alone, no patients are expected to experience a PSA < nadir + 2 ng/mL after cessation of ADT.

2.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine the rate of testosterone-PSA uncoupling (section 3.2.3.1) in each study arm in cohort 2.

Hypothesis: Combination therapy of pembrolizumab with RT with or without SD-101 leads to testosterone-PSA uncoupling in a subset of patients after discontinuation of therapies.

(2) **Objective:** To estimate time to clinical progression in each study arm in cohort 2.

Hypothesis: Combination therapy of pembrolizumab with RT with or without SD-101 leads to prolonged time to clinical progression in a subset of patients after discontinuation of therapies.

(3) **Objective:** To estimate progression-free survival (PFS) in each study arm in cohort 2.

Hypothesis: Combination therapy of pembrolizumab with RT with or without SD-101 leads to improved PFS compared to historical controls in a subset of patients after discontinuation of therapies.

2.3 Exploratory Objectives

(1) **Objective:** To assess peripheral and tumor-based biomarkers of response and resistance for both cohorts.

(2) **Objective:** To define the treatment-induced effects on circulating immune cells for both cohorts.

(3) **Objective:** To explore the remodeling of circulating T cell repertoire for both cohorts.

(4) **Objective:** To explore the concordance of PSMA-PET scanning with conventional imaging in oligometastatic prostate cancer patients for both cohorts.

3.0 BACKGROUND & RATIONALE

3.1 Background

Prostate cancer is the most common malignancy and the second leading cause of cancer-related death in men in Western countries. In the United States, 233,000 new cases were diagnosed and nearly 30,000 men died from prostate cancer in 2014 (Siegel R et al, 2014). While surgery and radiotherapy are potentially curative treatments in patients with localized prostate cancer, androgen deprivation therapy (ADT) is the mainstay of therapy for patients with hormone-sensitive metastatic prostate cancer. The duration of response to ADT is variable, and patients eventually develop castration-resistant disease (CRPC).

The development of novel hormonal agents, including abiraterone acetate and enzalutamide, has significantly improved outcomes for patients with metastatic CRPC (de Bono JS et al, 2011; Ryan CJ et al, 2013; Scher HI et al, 2012; Beer TM et al, 2014). However, resistance eventually develops, and emerging evidence suggest that these novel androgen signaling inhibitors may promote the development of more aggressive forms of prostate cancer with neuroendocrine features (Small EJ et al, 2015). Immunotherapeutic approaches, which do not target cancer cells directly but targets the patient's immune response to recognize and attack cancer, have the potential to lead to durable responses without driving mechanisms of resistance in advanced prostate cancer.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

3.1.1 Pharmaceutical and Therapeutic Background

3.1.1.1 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Pharmacokinetics and Metabolism of Pembrolizumab

The PK profile of pembrolizumab investigated in Part A of the ongoing study P001 has obtained results following a single dose at 1, 3, and 10 mg/kg pembrolizumab to 17 subjects with solid tumors in Cycle 1. The observed PK profile of pembrolizumab was typical of those observed for other IgG mAbs with a half-life ($t_{1/2}$) of approximately 2 to 3 weeks. There was no indication of dose dependency of $t_{1/2}$ in the 3 dose groups. A dose-related increase in exposure was observed from 1 to 10 mg/kg. The long $t_{1/2}$ supports a dosing interval of every 2 weeks or every 3 weeks.

No traditional metabolism studies were conducted with pembrolizumab per current ICH S6 (R1) guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals. Pembrolizumab has a low potential of eliciting the formation of anti-drug antibodies.

Toxicity and Safety Pharmacology of Pembrolizumab

The safety of pembrolizumab was characterized in the 1-month repeat-dose toxicity study in Cynomolgus monkeys when administered as IV doses of 6, 40, or 200 mg/kg once a week (a total of 5 doses) and in the 6-month repeat-dose toxicity study in Cynomolgus monkeys when administered as IV doses of 6, 40, or 200 mg/kg every other week (a total of 12 doses). Pembrolizumab was well-tolerated in Cynomolgus monkeys with a systemic exposure (AUC) of up to approximately 170,000 µg.day/mL over the course of the 1-month study and with a systemic exposure (AUC) of up to approximately 67,500 µg.day/mL over the course of the 6-month study. No findings of toxicological significance were observed in either 1-month or 6-month toxicity study with pembrolizumab, and the NOAEL was = 200 mg/kg. In addition, no findings of toxicological relevance were observed in the in vitro tissue cross-reactivity study using human and Cynomolgus monkey tissues. There were no nonclinical findings that would preclude testing of pembrolizumab in clinical trials.

3.1.1.2 SD-101

SD-101 is an oligodeoxynucleotide (ODN) enriched with cytidine-phospho-guanosine (CpG) motifs of Class C-type sequence (CpG-C). The CpG-C type sequences are an agonist for Toll-like receptor 9 (TLR9) and potent inducers of interferon alpha (IFN-α) production from plasmacytoid dendritic cells (pDCs), as well as pDC maturation and B cell proliferation. TLR9 stimulation by CpG-ODNs may have a significant antitumor effect by several potential mechanisms including enhancement of innate and T-cell immunity, stimulation of cytokines with direct or indirect antitumor activities (including IFN-α), and production of cytotoxic antibodies (Marshall JD et al, 2003; Marshall JD et al, 2005). Preclinical mouse models show that the combination of CpG therapy with checkpoint blockade enhances tumor regression and long-term survival (Mangsbo SM et al, 2010; Duraiswamy J et al, 2013).

Pharmacokinetics and Metabolism of SD-101

In the healthy normal volunteer trial, 20 subjects (18 years and older) were given a single fixed subcutaneous (SC) dose of SD-101 (0.1, 1.0, 3.0, or 5.0 mg) or placebo, SD-101 levels in the plasma peaked 2 to 4 hours after drug administration. The mean maximum plasma concentration for 6 subjects injected with SD-101 3.0 mg was approximately 7 ng/mL and was higher than for subjects receiving SD-101 1.0 mg. The SD-101 levels in plasma declined after 4 hours. Due to limitations in the analytical method such as a lower limit of quantitation of 5 ng/mL and analyte stability in matrix, the data provided are for information only. The dataset was insufficient for the calculation of parameters such as clearance rate or half-life.

Toxicity and Safety Pharmacology of SD-101

Three toxicity studies have been performed with SD-101, including a 14 once-weekly dose subcutaneous (SC) study in rats, a 14 once-weekly dose SC study in monkeys, and a safety pharmacology SC study in monkeys. No significant safety concerns have been identified in any of the toxicity studies conducted to date with SD-101. Genotoxicity studies indicated that SD-101 has no mutagenic or clastogenic activity.

Nearly all of the findings in the toxicity studies conducted with SD-101 were expected and consistent with the known properties of immunostimulatory ODNs, or the known class effects of PS ODNs. Also the effects of SD-101 were more pronounced in rats than in non-human primates. As an immunostimulatory molecule, SD-101 would be expected to induce reactivity of lymphoid tissues (i.e. spleen and lymph nodes), as well as immunocompetent cells in other organs in the clinical dose range. At higher dose levels, the effects on target tissues are exaggerated, well understood, dose-dependent, and reversible.

3.1.2 Preclinical and Clinical Trial Data

3.1.2.1 Pembrolizumab

Refer to the Investigator's Brochure for pembrolizumab for complete Preclinical and Clinical data.

The safety and efficacy of pembrolizumab in subjects with hematologic malignancies and solid tumors have been evaluated in 18 ongoing, Merck-sponsored clinical trials: P001, P002, P006, P010, P011, P012, P013, P021, P022, P023, P024, P025, P028, P029, P030, P041, P045, and P055.

P001: P001 is an open-label, Phase I, first-in-human (FIH) study of IV pembrolizumab in subjects with progressive locally advanced or metastatic carcinomas, especially melanoma or NSCLC.

Part A of the study involved dose escalation that used a traditional 3+3 design. Cohorts of 3 to 6 subjects were enrolled sequentially at escalating doses of 1, 3, or 10 mg/kg administered Q2W.

Once the dose escalation was completed, additional subjects were enrolled into Parts A1 and A2 to further characterize the PK and pharmacodynamics of pembrolizumab.

In Parts B and D, subjects with metastatic melanoma were enrolled to assess the safety and antitumor activity of pembrolizumab. Additionally, Part B explored 3 different dose regimens in subjects with metastatic melanoma: 10 mg/kg Q2W, 10 mg/kg Q3W, and 2 mg/kg Q3W.

In Part C, subjects with NSCLC (with prior systemic therapy) were enrolled at 10 mg/kg Q3W to assess the tolerability, safety, and antitumor activity of pembrolizumab in NSCLC.

In Part F, subjects with NSCLC in Cohort F-1 (without prior systemic therapy) and Cohort F-2 (with prior systemic therapy), whose tumors expressed PD-L1, were enrolled at 10 mg/kg Q2W and 10 mg/kg Q3W to characterize the tolerability, safety, and antitumor activity of pembrolizumab. A small cohort of previously treated subjects with NSCLC and at least 2 lines of systemic therapy, whose tumors did not express PD-L1, were enrolled and treated at a dose of 10 mg/kg Q2W in Cohort F-2. In Cohort F-3, previously treated subjects with NSCLC whose tumors express PD-L1 were enrolled at 2 mg/kg Q3W to better characterize the efficacy, safety, and antitumor activity of pembrolizumab.

Each of the 2 disease specific cohorts (melanoma and NSCLC) were enrolled to confirm tolerability and evaluate tumor response to pembrolizumab.

P002: P002 is a partially blinded, randomized, Phase II study designed to evaluate 2 doses of pembrolizumab versus a chemotherapy control arm in subjects with IPI-refractory metastatic melanoma. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab 2 mg/kg Q3W or pembrolizumab 10 mg/kg Q3W, or chemotherapy (according to current clinical practice) for the treatment of melanoma. Subjects assigned to the control chemotherapy arm could cross over to the experimental pembrolizumab arm once progression was confirmed (approximately = Week 12).

P006: P006 is a multicenter, worldwide, randomized, controlled, open-label, 3-arm pivotal Phase III study of 2 dosing regimens of IV pembrolizumab versus IV IPI in subjects with unresectable or metastatic melanoma who had not received prior IPI treatment. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab at 10 mg/kg Q2W, 10 mg/kg Q3W, or IPI at 3 mg/kg Q3W for a total of 4 doses.

P010: P010 is a multicenter, worldwide, randomized, adaptively designed Phase II/III trial of IV pembrolizumab at 2 dosing schedules versus docetaxel in subjects with NSCLC with PD-L1 positive tumors, who have experienced disease progression after platinum-containing systemic therapy. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab 10 mg/kg Q3W, 2 mg/kg Q3W, or docetaxel 75 mg/m^2 Q3W.

P011: P011 is an open-label, nonrandomized, multicenter Phase I study of pembrolizumab monotherapy in Japanese subjects with advanced solid tumors and in combination with cisplatin/pemetrexed and carboplatin/paclitaxel in subjects with advanced NSCLC in Japan.

In Part A (monotherapy, 3+3 design), subjects with advanced solid tumors received escalating doses of pembrolizumab 2 mg/kg Q2W (dose level 1) or 10 mg/kg Q2W (dose level 2). In Part B (combination, 3+6 design), subjects with advanced NSCLC receive pembrolizumab 10 mg/kg Q3W in combination with either cisplatin/pemetrexed (Cohort 1) or carboplatin/paclitaxel (Cohort 2) are to be enrolled.

P012: P012 is a multicenter, nonrandomized, multi-cohort Phase Ib trial of pembrolizumab in subjects with PD-L1 positive advanced solid tumors. All subjects receive pembrolizumab 10 mg/kg Q2W. Cohort A enrolled subjects with triple negative breast cancer; Cohorts B and B2 enrolled subjects with squamous cell carcinoma of the head and neck; Cohort C enrolled subjects with urothelial tract cancer of the renal pelvis, ureter, bladder, or urethra; and Cohort D enrolled subjects with adenocarcinoma of the stomach or gastroesophageal junction.

P013: P013 is an open-label, multicenter trial of pembrolizumab in subjects with hematologic malignancies. All subjects receive pembrolizumab at 10 mg/kg Q2W. Cohort 1 is enrolling subjects with intermediate-1, intermediate-2, or high-risk myelodysplastic syndrome who have failed at least 4 cycles of hypomethylating agent treatment. Cohort 2 is enrolling subjects with relapsed/refractory multiple myeloma. Cohort 3 is enrolling subjects with relapsed/refractory Hodgkin lymphoma who are ineligible for or refused a stem cell transplant and whose disease has relapsed after treatment with or failed to respond to brentuximab vedotin. Cohort 4a is enrolling subjects with relapsed/refractory mediastinal large B cell lymphoma who are ineligible for or refused a stem cell transplant, and Cohort 4b is enrolling subjects with any other positive PD-L1 positive relapsed/refractory non-Hodgkin lymphoma who are ineligible for or refused a stem cell transplant.

P021: P021 is a multicenter, open-label Phase I/II study of IV pembrolizumab at 2 dosing schedules in combination with chemotherapy or immunotherapy in subjects with locally advanced or metastatic NSCLC. The study is composed of 2 parts.

The objective of Part 1 is to determine the recommended Phase II dose (RP2D) for pembrolizumab in combination with different chemotherapy and/or immunotherapy regimens:

- Cohort A – 1:1 randomization to carboplatin and paclitaxel plus either pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg
- Cohort B – 1:1 randomization to carboplatin, paclitaxel, and bevacizumab plus either pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg
- Cohort C – 1:1 randomization to carboplatin and pemetrexed plus either pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg
- Cohort D – ipilimumab plus pembrolizumab
- Cohort E – erlotinib plus pembrolizumab
- Cohort F – gefitinib plus pembrolizumab

The objective of Part 2 is to evaluate the antitumor activity of pembrolizumab in combination with chemotherapy or immunotherapy. Part 2 includes a randomized comparison of chemotherapy ± pembrolizumab based on the doses defined in Part 1, as well as a cohort expanding the ipilimumab cohort from Part 1:

- Cohort G – 1:1 randomization to carboplatin and pemetrexed with or without pembrolizumab 200 mg
- Cohort H – ipilimumab (RP2D from Part 1 Cohort D) plus pembrolizumab, followed by pembrolizumab monotherapy

P022: P022 is a multicenter, worldwide, Phase I/II 3-part trial of IV pembrolizumab in combination with oral dabrafenib and/or trametinib in subjects with advanced or metastatic melanoma.

Part 1 is a non-randomized, multi-site, open-label portion of the study using a traditional 3+3 design to evaluate safety, tolerability, and dosing of pembrolizumab (MK) in combination with dabrafenib (D) and trametinib (T) in BRAF mutation-positive (V600 E or K) melanoma subjects. Additionally in Part 1, dosing of pembrolizumab in combination with trametinib only (MK+T) will be explored in BRAF mutation-negative (without V600 E or K) melanoma subjects, to evaluate safety, tolerability, and efficacy of MK+T in Part 2 in this population. Part 2 is a non-randomized, multisite, open-label portion of the study using an expansion cohort to further evaluate safety and confirm dose of MK+D+T. Also in Part 2, an expansion cohort will be used to further evaluate safety and preliminary efficacy in the MK+T combination. Part 3 is a randomized (1:1), active-controlled, multi-site, 2-arm study of the confirmed dose of the triplet combination (MK+D+T) versus placebo (PBO) in combination with D+T (PBO+D+T).

P023: P023 is an open-label, Phase I, multicenter, trial of pembrolizumab in combination with lenalidomide (Len) and dexamethasone (Dex) or pembrolizumab and Len in subjects with relapsed/refractory multiple myeloma who have failed at least 2 lines of prior therapy, including a proteasome inhibitor (e.g., bortezomib or carfilzomib) and an immunomodulary derivative (thalidomide, pomalidomide, lenalidomide). The trial uses a modified 3+3 design for dose determination, followed by dose confirmation and expansion, a further evaluation of safety, and a preliminary assessment of efficacy. During dose determination, cohorts of approximately 3 to 6 subjects are enrolled and receive pembrolizumab 2 mg/kg or 1 mg/kg IV Q2W in each 28-day cycle, in combination with Dex 40 mg QW and/or Len 25 mg or 10 mg on Days 1 to 21. After a preliminary MTD/maximum administered dose (MAD) is identified, additional subjects are enrolled at a fixed dose of pembrolizumab 200 mg or 100 mg in combination with Len/Dex to confirm the MTD/MAD.

P024: P024 is a multicenter, international, randomized, open-label trial of IV pembrolizumab monotherapy vs the choice of multiple, standard-of-care, platinum-based chemotherapies in subjects previously untreated for their Stage IV, PD-L1 strong, NSCLC. All subjects are randomized in a 1:1 ratio to receive pembrolizumab at 200 mg IV Q3W or 1 of the 5 following platinum doublets:

- Pemetrexed at 500 mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4 to 6 cycles followed by optional pemetrexed 500 mg/m2 Q3W
- Pemetrexed 500 mg/m^2 Q3W and cisplatin 75 mg/m^2 day 1 Q3W for 4 to 6 cycles followed by optional pemetrexed 500 mg/m2 Q3W

- Gemcitabine 1250 mg/m^2 days 1 and 8 and cisplatin 75 mg/m^2 day 1 Q3W for 4 to 6 cycles
- Gemcitabine 1250 mg/m^2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4 to 6 cycles
- Paclitaxel 200 mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4 to 6 cycles followed by optional pemetrexed maintenance

P025: P025 is an open-label, non-randomized, multicenter Phase Ib study of pembrolizumab in Japanese subjects with positive PD-L1 advanced NSCLC in Japan. All subjects received pembrolizumab at 10 mg/kg Q3W.

P028: P028 is an open-label, non-randomized, multicenter, multicohort Phase Ib trial of pembrolizumab in subjects with PD-L1 positive advanced solid tumors. Subjects are enrolled into 1 of the following 20 solid tumor cohorts: A1 Colon or Rectal Adenocarcinoma; A2 Anal Canal Squamous Cell Carcinoma; A3 Pancreas Adenocarcinoma; A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction); A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers); A6 Carcinoid Tumors; A7 Neuroendocrine Carcinomas (well or moderately differentiated Pancreatic Neuroendocrine Tumor); B1 ER Positive HER2 Negative Breast Cancer; B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma; B3 Endometrial Carcinoma; B4 Cervical Squamous Cell Cancer; B5 Vulvar Squamous Cell Carcinoma; C1 Small Cell Lung Cancer; C2 Mesothelioma (Malignant Pleural Mesothelioma); D1 Thyroid Cancer (Papillary or Follicular Subtype); D2 Salivary Gland Carcinoma; D3 Nasopharyngeal Carcinoma; E1 Glioblastoma Multiforme E2 Leiomyosarcoma; or E3 Prostate Adenocarcinoma. All subjects receive pembrolizumab 10 mg/kg Q2W.

P029: P029 is a multicenter, open-label, 3-part Phase I/II trial of IV pembrolizumab in combination with subcutaneous Pegylated Interferon Alfa-2b (PEG-IFN) or IV IPI in subjects with advanced or metastatic melanoma or renal cell carcinoma. Part 1A, the Phase I portion of the trial, will define the preliminary MTD or MAD of pembrolizumab + PEG-IFN (Group A) and pembrolizumab + IPI (Group B), and confirm the tolerability of these treatment doublets.

Part 1B is a single-arm expansion cohort designed to better characterize the safety and tolerability, as well as to evaluate preliminary efficacy of the pembrolizumab + IPI combination in melanoma subjects. Part 2, the randomized portion of the trial, will evaluate preliminary clinical efficacy in advanced melanoma at the RP2D for pembrolizumab + PEG-IFN and the Phase II Dose determined in Part 1A and 1B for pembrolizumab + IPI. Evaluation of pembrolizumab monotherapy may also occur during Part 2.

P030: P030 is a multisite, worldwide, expanded access program for subjects with metastatic melanoma who have limited or no treatment options. Subjects must have progressed after prior systemic therapy, including standard-of-care agents which include IPI and a BRAF/MEK inhibitor when indicated. Subjects cannot be eligible for an available pembrolizumab clinical trial or have participated in a pembrolizumab clinical trial. Subjects are evaluated for safety at baseline and before each cycle of treatment with pembrolizumab 2 mg/kg/Q3W. Subjects are treated until progression of disease or until the subject has received up to 2 years of treatment.

P041: P041 is an open-label, nonrandomized, multicenter Phase Ib study to evaluate the safety, tolerability, and antitumor activity of treatment with pembrolizumab 2 mg/kg Q3W in subjects with advanced melanoma in Japan. Treatment with pembrolizumab will continue unless a subject meets the discontinuation criteria such as disease progression (evaluated by modified Response Evaluation Criteria In Solid Tumors [RECIST] 1.1), unacceptable toxicity, or completion of 24 months of treatment with pembrolizumab.

P045: P045 is a randomized, active-controlled, multisite, open-label, Phase III trial to evaluate the efficacy of treatment with pembrolizumab versus paclitaxel, docetaxel, or vinflunine in subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy. Subjects are randomized in a 1:1 ratio to receive pembrolizumab 200 mg Q3W or the Investigators' choice of paclitaxel 175 mg/m^2 Q3W, docetaxel 75 mg/m^2 Q3W, or vinflunine 320 mg/m^2 Q3W. The study also evaluates the safety and tolerability profile of pembrolizumab in subjects with recurrent/progressive metastatic urothelial cancer.

P055: P055 is a multicenter, unblinded, open-label, single-cohort, Phase II trial to determine the safety, tolerability, and antitumor activity of a 200 mg Q3W dose of pembrolizumab in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy. Antitumor activity is also assessed in the subset of subjects for whom a biopsy sample is determined to be PD-L1 positive.

3.1.2.2 SD-101

Refer to the Investigator's Brochure for SD-101 for complete Preclinical and Clinical data.

TriSalus Life Sciencesclinical trials in healthy normal volunteers and in patients with chronic HCV infection have concluded, and results are summarized below. One phase 1 trial in patients with low-grade untreated NHL (DV3-LYM-01) is ongoing. In DV3-LYM-01, 3 patients have received 5 intratumoral doses of SD-101 1.0 mg, and 3 patients have received 5 intratumoral doses of SD-101 2.0 mg without DLT. The most common AEs were transient flu-like illness. In the initial dose-escalation study with melanoma, SD-101 will be administered by intratumoral injection with doses from 2.0 mg to 8.0 mg, and these doses are at least 67-fold below the NOAEL in monkeys. Based on the extensive clinical experience with another CpG-ODN administered by intratumoral injection (Brody JD et al, 2010; Kim YH et al, 2012), in addition to the tolerability of SD-101 demonstrated to date, no major local reactions are expected with intratumoral injections of SD-101. It is expected that intratumoral injection of SD-101 (at maximal proposed doses up to 0.12 mg/kg for a 65 kg person) will result in a similar acceptable safety profile. Therefore, the dose of 2 mg SD-101 is expected to be safe and effective, and was chosen for this study.

Healthy Normal Volunteer Trial (DV3-HNV-01)
Trial DV3-HNV-01, A Phase 1, Randomized, Single-Blind, Placebo-Controlled Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of SD-101 in Healthy Normal Male Volunteers was completed at 1 trial site and enrolled 26 subjects.

In this trial, 20 subjects (18 years and older) were given a single fixed SC dose of SD-101 or placebo and were evaluated for safety, tolerability, PK, biomarker activation (type I IFN-inducible gene expression and serum protein levels), blood lymphocytes, and dendritic cells (DC) subsets. Fixed escalating doses of SD-101 (0.1, 1.0, 3.0, or 5.0 mg) were administered as follows: 2 subjects were treated at a dose level; if no dose-limiting toxicity (DLT; any SD-101-related SAE, any single Grade 3, 4, or 5 toxicity, or any unexpected Grade 2 toxicity) occurred, then 8 additional subjects were randomized in a single-blind fashion: 4 to the dose level being tested, 2 to placebo, and 2 to the next higher dose. Six subjects were enrolled at each of the 0.1, 1.0, and 3.0 mg dose levels, 6 additional subjects received placebo, and 2 subjects were enrolled to the 5.0 mg dose level before the trial was halted for DLTs.

Overall, 24 (92.3%) subjects reported 80 AEs. Of these AEs, 77.5% were assessed by the investigator as Grade 1 (mild), 17.5% were assessed as Grade 2 (moderate), and 5% were assessed as Grade 3 (severe). There were no Grade ≥4 AEs and no SAEs in this trial. The most frequently reported AEs were classified within the System Organ Classes (SOC) of blood and lymphatic system disorders, general disorders, and administration site conditions. One (1) subject at the 5.0 mg dose level experienced Grade 3 neck pain, headache, and a 10-cm injection-site induration. These 3 events were considered DLTs, and the trial was interrupted and subsequently concluded per the protocol's stopping rule. Additional AEs included influenza-like symptoms such as headache, chills, fatigue, and pyrexia, as well as injection site events such as erythema, induration, and pain.

No subject showed evidence of complement activation or autoantibody (anti-dsDNA or anti-nuclear antibody) formation. Transient lymphopenia was the most common laboratory abnormality observed, although transient thrombocytopenia and neutropenia were also reported in 2 subjects and 1 subject, respectively.

Trial in Patients with HCV Infection (DV3-HCV-01)

Trial DV3-HCV-01, A Phase 1, Randomized, Single-Blind, Placebo-Controlled Dose-Escalation Study of SD-101 to Assess the Safety, Pharmacodynamics, and Preliminary Evidence of Anti-Viral Effect in Subjects Diagnosed with Chronic Hepatitis C, Genotype 1, was completed at 4 study sites and enrolled 34 patients.

This was a trial of 4 fixed SC doses (0.1, 1.0, 3.0, and 5.0 mg) of SD-101 in 34 male and female patients (age 18-55 years) (28 patients in SD-101 and 6 patients in placebo). The planned treatment schedule was as follows: 4 weeks of once-weekly SD-101 alone or placebo, followed by 8 weeks of a combined once-weekly fixed dose of SD-101 or placebo and ribavirin, followed by 12 weeks of standard-of-care treatment (pegylated IFN--2a and ribavirin). Viral load assessment was conducted at specified time points through Week 25. If at Week 25 patients compared with Week 13, treatment with standard-of-care (pegylated IFN--2a and ribavirin) was provided by **TriSalus Life Sciences**to continue for a total of 48 weeks.

Overall, during the combined dosing periods (study drug or placebo monotherapy and with ribavirin), 32 (94.1%) patients, including 27 patients treated with SD-101 at any dose and

5 patients treated with placebo, reported an AE. The most frequently reported AEs by Preferred Term were injection site pain, injection site erythema, injection site swelling, and injection site pruritus. In general, injection site reactions were noted with high frequency in all dose groups, including the placebo group. Influenza-like symptoms, pyrexia, and myalgia were the most frequently reported non-injection site reactions overall.

Most AEs were Grade 1 or 2 (mild to moderate) in severity. There were no Grade 4 AEs. Grade 3 events were reported in the patient with an SAE (hyperthyroidism), who had received 8 doses of SD-101 0.1 mg. [redacted].

One additional patient who had received 12 doses of SD-101 1.0 mg (and was receiving pegylated IFN- and ribavirin at the time of the AE) was discontinued by the investigator due to a reported AE, positive test for anti-dsDNA, not associated with other symptoms or signs of complications related to the positive ds-DNA. The patient was negative for anti-dsDNA at the Discontinuation Visit.

Trial in Patients with Untreated Low-Grade B-Cell Lymphomas (DV3-LYM-01)
Trial DV3-LYM-01, A Phase 1/2, Non-randomized, Open-label, Multicenter, Dose Escalation and Expansion Study of Intratumoral Injections of SD-101 in Combination With Localized Low-dose Radiation in Patients With Untreated Low-grade B-cell Lymphoma

This is a phase1/2, non-randomized, open-label, multicenter, dose-escalation, and expansion trial designed to evaluate the safety and preliminary efficacy of localized low-dose XRT and intratumoral SD-101 injection into a single target lesion ("Lesion A") in patients with untreated low-grade B-cell lymphomas who do not require immediate systemic therapy and are appropriate candidates for "watch and wait". This trial is being conducted in 2 parts. Part 1 (Dose Escalation) consists of the evaluation of 4 escalating dose levels, and Part 2 (Expansion) includes enrollment of additional patients at the MTD or optimal dose level from Part 1.

To date, 3 patients have received 5 intratumoral doses of SD-101 1.0 mg, and 3 patients have received 5 intratumoral doses of SD-101 2.0 mg. No DLT was observed, and the most common AEs were transient flu-like illness in the 2.0 mg cohort. Dosing at 4.0 mg is planned but has not yet begun.

Trial in Patients with Recurrent Lymphoma following Allogeneic Hematopoietic Cell Transplantation (Investigator-Sponsored Trial at Stanford University Medical Center)
IND 111985: Intratumoral Injection of SD-101 Combined with Local Radiation for the Treatment of Recurrent or Progressive Lymphoma After Allogeneic Hematopoietic Cell Transplantation.

In this investigator-sponsored dose-escalation trial, up to 18 patients will receive 2 doses of RT (4 Gy) over 2 days and then received 3 weekly doses of SD-101 in a standard 3+3 design. SD-101 is administered intratumorally using the following doses: 0.3 mg, 1.0 mg, and 3.0 mg. To date, 3 patients received 3 weekly intratumoral doses of SD-101 0.3 mg and 2 patients received 3

weekly intratumoral doses of SD-101 1.0 mg. One unrelated SAE of Klebsiella bacteremia was reported in a patient who received SD-101 1.0 mg. No other AEs have been reported (**TriSalus Life Sciences**personal communication with investigator).

SD-101, Radiation, and Ipilimumab Trial in Patients with Relapsed Lymphoma (Investigator Sponsored Trial at Stanford University Medical Center)
IND 111985: A Phase I/II Study of Intratumoral Injection of SD-101, an Immunostimulatory CpG, and intratumoral Injection of Ipilimumab, an anti-CTLA4 Monoclonal Antibody, in Combination with Local Radiation in Low-Grade B-cell Lymphomas

In this investigator-sponsored dose-escalation of ipilimumab trial, up to 12 patients will receive 2 doses of RT (4 Gy) over 2 days and then receive 1 intratumoral dose of ipilimumab (5, 10, or 25 mg), and 5 weekly doses of 1 mg of SD-101 intratumorally in a standard 3+3 design. This trial is ongoing but no patients have been treated as of 1 March 2015.

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Subject Population

Prostate cancer is a target of the host immune response. Multiple treatment factors play into this immune response, which is a complex, constantly changing equilibrium affected by radiation therapy, androgen deprivation therapy, and checkpoint regulation. With radiation therapy and androgen deprivation therapy, increased effector T-cell infiltration is observed within the prostate gland and tumor(s). However, effector T cell infiltration is often transient due, in part, to the tumor's ability to activate immune checkpoints. New agents targeting checkpoint inhibition help to combat the immunosuppression. Specifically, drugs targeting the PD-L1/PD-1 checkpoint pathway have generated significant clinical interest in prostate cancer.

The PD-L1/PD-1 axis is a potent immune regulator through inhibition of effector T cell function. The PD-L1 protein is undetectable in most normal tissues, but can be induced by radiation. Although at baseline, prostate cancer expresses low levels of PD-L1, the T-cells that infiltrate the prostate gland highly express PD-1.[1, 2] A phase Ib trial investigated the efficacy of PD-1 blockade in 236 patients with various solid malignancies, included 17 patients with castration-resistant prostate cancer (CRPC). In 2 of the 17 patients, PD-L1 expression in tumor specimens were evaluated and were negative. Response to anti-PD-1 therapy may reflect the level of PD-L1 expression.[3] . Thus, a greater response may have been seen with induction of PD-L1 expression. However, we have assessed PD-L1 expression in a collaboration with the Johns Hopkins group, and can detect >5% PD-L1 staining by their scoring in approximately half of the prostatectomy specimens assessed from our neoadjuvant SipT trial. In addition, a recent study demonstrated that ionizing radiation increases tumoral expression of PD-L1. When anti-PD-L1 therapy was subsequently administered after irradiation (IR), a synergistic effect on tumor regression was observed. The concept of IR-induced PD-L1 expression and subsequent anti-PDL1/PD-1 blockade was suggested to broaden the application of PD-L1/PD-1 axis inhibitors leading to potent antitumor responses when combined with radiotherapy.[4]

Radiation therapy is commonly used to treat primary and metastatic tumors. As suggested above, radiation therapy may improve the therapeutic efficacy of checkpoint inhibition. Recent studies demonstrated that high-dose ablative radiotherapy triggers a rapid, adaptive immune response mediating tumor regression. Radiation therapy may be utilized to tip the balance toward a more robust anti-tumor response in combination with checkpoint inhibitor therapy than with the checkpoint inhibitor alone. Recent studies suggest that the combination of radiation therapy and checkpoint inhibitors may synergistically promote T-cell antitumor immunity and prolonged protective immunity.[4, 5] Moreover, the effects of combination radiation therapy and checkpoint inhibitor blockade have been visualized at secondary sites that did not receive radiotherapy (i.e., abscopal effect).

SD-101 is an oligodeoxynucleotide (ODN) enriched with cytidine-phospho-guanosine (CpG) motifs of Class C-type sequence (CpG-C). The CpG-C type sequences are an agonist for Toll-like receptor 9 (TLR9) and potent inducers of interferon alpha (IFN-α) production from plasmacytoid dendritic cells (pDCs), as well as pDC maturation and B cell proliferation. TLR9 stimulation by CpG-ODNs may have a significant antitumor effect by several potential mechanisms including enhancement of innate and T-cell immunity, stimulation of cytokines with direct or indirect antitumor activities (including IFN-α), and production of cytotoxic antibodies (Marshall JD et al, 2003; Marshall JD et al, 2005). Preclinical mouse models show that the combination of CpG therapy with checkpoint blockade enhances tumor regression and long-term survival (Mangsbo SM et al, 2010; Duraiswamy J et al, 2013).

The combination approach of radiation therapy, androgen deprivation therapy, SD-101, anti-PD-L1 therapy has not been well studied in prostate cancer. We hypothesize that the combination of PD-1 blockade (pembrolizumab) and localized therapies that prime and augment an immune response (definitive prostatic radiotherapy with or without intratumoral SD-101, an TLR9 agonist), will induce a durable clinical response in a subset of patients with metastatic hormone-sensitive prostate cancer, reflected by a prolonged period of PSA < nadir + 2 ng/mL after cessation of all therapies including ADT.

The study population of chemotherapy-naïve oligometastatic hormone-sensitive prostate cancer is selected based on emerging data that immunotherapy for prostate cancer is most likely to benefit patients with lower disease burden (Kwon ED et al, 2014), presumably due to a lower level of immunosuppression, both systemically and in the tumor microenvironment.

3.2.2 Rationale for Dose Selection/Regimen/Modification

3.2.2.1 Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test

for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

3.2.2.2 SD-101

Three toxicity studies have been performed with SD-101, including a 14 once-weekly dose subcutaneous (SC) study in rats, a 14 once-weekly dose SC study in monkeys, and a safety pharmacology SC study in monkeys. No significant safety concerns have been identified in any of the toxicity studies conducted to date with SD-101. Genotoxicity studies indicated that SD-101 has no mutagenic or clastogenic activity.

Nearly all of the findings in the toxicity studies conducted with SD-101 were expected and consistent with the known properties of immunostimulatory ODNs, or the known class effects of PS ODNs. Also the effects of SD-101 were more pronounced in rats than in non-human primates. As an immunostimulatory molecule, SD-101 would be expected to induce reactivity of lymphoid tissues (i.e. spleen and lymph nodes), as well as immunocompetent cells in other organs in the clinical dose range. At higher dose levels, the effects on target tissues are exaggerated, well understood, dose-dependent, and reversible.

TriSalus Life Sciencesclinical trials in healthy normal volunteers and in patients with chronic HCV infection have concluded, and one phase 1 trial in patients with low-grad untreated NHL is ongoing. In the NHL study, 3 patients have received 5 intratumoral doses of SD-101 1.0mg, and 3 patients have received 5 intratumoral doses of SD-101 2.0mg without DLT. The most common AEs were transient flu-like illness. In the initial dose-escalation study with melanoma, SD-101 will be administered by intratumoral injection with doses form 2.0mg to 8.0mg, and these doses are at least 67-fold below the NOAEL in monkeys. Based on the extensive clinical experience with another CpG-ODN administered by intratumoral injection (Brody JD et al, 2010; Kim YH et al, 2012), in addition to the tolerability of SD-101 demonstrated to date, no major local reactions are expected with intratumoral injections of SD-101. It is expected that intratumoral injection of SD-101 (at maximal proposed doses up to 0.12 mg/kg for a 65 kg person) will result in a similar acceptable safety profile. Therefore, the dose of 5 mg SD-101 is expected to be safe and effective, and was chosen for this study.

3.2.2.3 Radiotherapy

Radiotherapy (RT) has the potential to enhance anti-tumor effects of immune checkpoint blockade by multiple mechanisms, including providing antigen presentation, releasing proinflammatory signals from dying tumor cells, and enhancing the diversity of TCR repertoire of intratumoral T cells (Cha E et al, 2010; Twyman-Saint Victor C et al, 2015). Preclinical mouse models have shown that the combination of RT with immunotherapies can enhance anti-tumor efficacy and improve long-term survival, including in glioma, melanoma and breast cancer (Belcaid Z et al, 2014; Twyman-Saint Victor C et al, 2015; Demaria S et al, 2005). There is evidence that RT produces more immune-mediated effect when given fractionated compared to in a single-dose (Dewan MZ et al, 2009; Vanpouille-Box CI et al, 2015).

In this study, RT to the whole prostate and soft tissue oligometastatic sites will be delivered via SBRT at a dose of 7 Gy x 5 fractions to a total of 35 Gy. RT to osseous metastases will be delivered via SBRT at a dose of 10 Gy x 3 fractions to a total of 30 Gy. RT will start 1-5 weeks after fiducial marker placement and SBRT simulation, and will be delivered every other day so that the last treatment will be 10-21 days after the start of SBRT. Intratumoral 5 mg SD-101

injection will be performed at the time of fiducial marker placement, and 1-3 weeks after C1D1. This prostate and soft tissue oligometasis-directed SBRT dose and fractionation scheme is chosen because it is an option for radiation with definitive intent in localized prostate cancer (Kishan AU & King CR, 2017). The dose and fractionation scheme for osseous oligometastases is chosen based on its established safety and efficacy in a prior randomized trial of oligometastasis-directed SBRT (Ost P et al, 2017). This dose and fractionation is considered ablative, and ablative dosing is hypothesized to transform an immunosuppressive tumor microenvironment to an immunogenic tumor microenvironment (Lee Y et al, 2009; Filatenkov A et al, 2015).

3.2.2.4 Androgen deprivation therapy

Subjects will receive intermittent androgen deprivation therapy consisting of 3 months of ADT run-in, followed by 9 months of GnRH targeting agent (leuprolide preferred), abiraterone, and prednisone (or equivalent), then discontinuation of ADT. A large, randomized phase III study did not demonstrate a significant difference in overall survival in patients receiving intermittent androgen deprivation therapy when compared with continuous androgen deprivation therapy. Of note, there were too few events to rule out non-inferiority of intermittent therapy when compared to continuous androgen deprivation therapy. Intermittent androgen therapy was associated with small improvements in quality of life including erectile function and mental health at month 3 (Hussain M et al, 2014). Furthermore, meta-analyses of randomized control trials have not shown a survival difference between intermittent and continuous ADT (Botrel TE et al, 2014, Niraula S et al, 2013). Therefore, intermittent androgen therapy has been accepted as a standard of care regimen in patients with metastatic prostate cancer. The withdrawal of androgen deprivation therapy with recovery of testosterone levels will allow us to evaluate the effect of the treatment regimen on the PSA response.

Subjects who have received less than 2 months of ADT prior to screening are eligible for the study. To ensure homogenous treatment among patients and to allow for scheduling of SBRT with or without SD-101 therapy (depending on study arm), subjects will have a 3 month period of ADT run-in prior to Cycle 1 Day 1. Subjects will start C1D1 and SBRT 1 month after ADT initiation at the earliest, and 4 months after ADT initiation at the latest.

Combined androgen blockade with GnRH targeting agent, abiraterone, and prednisone (or equivalent) PO daily are preferred and will be started for patients who have not received any ADT at time of screening. For subjects who have been started on leuprolide or another GnRH agent at time of screening, they will continue the respective GnRH agent for the remainder of ADT run-in (3 months total, accounting for duration of ADT prior to screening). They will continue this GnRH agent for the subsequent 9 months.

Subjects who were not on an antiandrogen, or were on an antiandrogen other than abiraterone at time of screening are required to start or switch to abiraterone (e.g. Zytiga, Yonsa) with prednisone (or equivalent) daily, respectively. They will continue abiraterone (e.g. Zytiga, Yonsa) daily with prednisone (or equivalent) daily for the remaining duration of ADT run-in and for 9 months starting on Cycle 1 Day 1.

3.2.3 Rationale for Endpoints

The **primary endpoint** is to determine the percentage of patients in cohort 2 who achieve PSA < nadir + 2 ng/mL at 15 months from the start of treatment who have non-castrate testosterone levels, where non-castrate testosterone level is defined as testosterone >150 ng/dL.

This primary endpoint is selected because we anticipate that at least 2 patients in each arm in cohort 2 will achieve non-castrate testosterone (>150 ng/dL) at 15 months from the start of treatment. PSA rise of 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after definitive radiation with or without hormonal therapy for patients with localized prostate cancer. In patients with metastatic hormone-sensitive prostate cancer who have ceased all therapies including ADT with testosterone recovery, PSA will almost certainly rise to above nadir + 2 ng/mL, without a significant and durable clinical benefit from immunotherapy. Therefore, the primary endpoint serves as a surrogate marker for the clinical activity of combination immunotherapy in this study with intermittent ADT.

3.2.3.1 Efficacy Endpoints

The following **secondary endpoints** were chosen to further assess the clinical activity of pembrolizumab combined with RT with or without SD-101 in patients with hormone-sensitive oligometastatic prostate cancer receiving intermittent androgen deprivation. Testosterone-PSA uncoupling serves as a less stringent assessment of PSA response in comparison to the primary endpoint. Time to clinical progression and progression-free survival (PFS) are well established efficacy endpoints, but would require a significantly larger sample size to establish statistical significance.

- To determine the rate of testosterone-PSA uncoupling in patients in cohort 2 treated with RT + Pembrolizumab (Arm 1) and RT + Pembrolizumab + SD-101 (Arm 2), where uncoupling is defined as PSA less than 50% baseline for at least 3 months after testosterone recovers to >150 ng/dL after discontinuation of ADT.

- To estimate time to clinical progression, defined as radiographic progression by RECIST v1.1, symptomatic progressive disease, or PSA progression on therapy in participants in each study arm in cohort 2.

- To estimate progression-free survival (PFS) of participants in each arm in cohort 2, where PFS is a composite endpoint based on PSA progression, radiological progression, clinical deterioration, or death.

3.2.3.2 Biomarker Research

Intratumoral T-cell infiltration and PD-L1 expression have been shown to correlate with improved clinical outcomes after PD-1 and PD-L1 blockade in some clinical studies. Furthermore, we have shown that clinical responses to immune checkpoint therapy in patients with prostate cancer and melanoma are associated with the amplification of pre-existing immune response (Cha E, et al. 2014). Thus, we will explore the following biomarkers as exploratory endpoints in this study, and correlate results with clinical response and outcomes.

- To assess peripheral and tumor-based biomarkers of response and resistance by:
    - Immunohistochemistry of immune cell infiltrates on baseline biopsy tissues and optional progression biopsy tissues
    - Assessment of PD-L1 staining on tumor and tumor-infiltrating immune cells (IC) on baseline biopsy tissues and optional progression biopsy tissues
    - Exploration of gene signature in pre-treatment tumor biopsies that correlates with treatment response
- To define the treatment-induced effects on circulating immune cells by flow cytometry.
- To explore remodeling of circulating T cell repertoire in the tumor and blood by deep sequencing of VDJ regions of TCRs.

4.0 METHODOLOGY

4.1 Entry Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1.1 Diagnosis/Condition for Entry into the Trial

Patients must have histologically proven diagnosis of prostate cancer, with hormone-sensitive oligometastatic disease.

4.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have a performance status of 0 or 1 on the ECOG Performance Scale.
4. Histologically documented adenocarcinoma of the prostate
5. Oligometastatic disease. In order to be eligible, the patient must have a total of <4 metastatic bone and/or metastatic lymph node sites based on bone and/or soft tissue lesions as defined by any of the following:

a. Bone metastases will be defined by bone imaging. If the patient has technetium bone scan, and/or NaF PET performed, either study may be used for documenting metastases; both scans do not need to show the number of metastases required for study entry. For patients undergoing PSMA PET, only PSMA avid lesions that are consistent with metastasis will be counted as a site of metastasis.

b. Distant metastatic lymph node disease. A lymph node ≥1 cm in shortest dimension will be noted as involved with disease. Distant metastatic lymph nodes will be determined as any lymph nodes outside the confines of the true pelvis. For patients undergoing PSMA PET, only PSMA avid lesions that are consistent with metastasis will be counted as a site of metastasis.

c. Any other soft tissue lesion deemed by the physician to be consistent with distant metastatic disease. For patients undergoing PSMA PET, only PSMA avid lesions that have a CT or MRI correlate consistent with metastasis will be counted as a site of metastasis.

Note: Radiographic imaging performed as standard of care prior to obtaining informed consent and within 60 days of initiating study treatment may be used to assess oligometastatic disease during screening, rather than repeating scans. For patients who have started on ADT, they must have had imaging prior to initiation of hormonal therapy.

6. Treatment naïve, defined as less than 2 months of standard of care ADT (e.g. GnRH agonist or antagonist with or without antiandrogen, including abiraterone) for metastatic hormone-sensitive prostate cancer prior to enrollment (at time of consent)

7. No prior chemotherapy for prostate cancer

8. Not a candidate for or refuse chemotherapy

9. No prior prostatectomy or prostatic radiation

10. PSA >2 ng/mL at baseline or prior to initiation of hormonal therapy

11. Baseline testosterone >150 ng/dL if patient has not initiated hormonal therapy. For those patients who have already initiated hormonal therapy, baseline testosterone is not required.

12. Consent to undergo mandatory prostatic core biopsies at the time of fiducial marker placement and 1-3 weeks after C1D1 of pembrolizumab.

13. The effects of pembrolizumab on the developing human fetus is unknown. Men treated or enrolled on this protocol must agree to use adequate contraception prior to the first dose of study therapy, for the duration of the study participation, and for 120 days after the last dose of study therapy.

14. Demonstrate adequate organ function as defined in Table 1:.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

15. Subjects should agree to use an adequate method of contraception prior to the first dose of study therapy through 120 days after the last dose of study therapy.

    a. Their partners should also be encouraged to use proper method of contraception.

4.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Patients who are not appropriate candidates for prostate-directed SBRT (cohort 1), or prostate and oligometastasis-directed SBRT (cohort 2).

2. Patients with neuroendocrine or small cell features are not eligible.

3. Patients with evidence of liver metastasis are excluded.

4. GnRH agonists or GnRH antagonists (e.g., leuprorelin, degarelix) for > 2 months prior to consenting

5. Antiandrogens (e.g., bicalutamide, flutamide, nilutamide, abiraterone, enzalutamide) for > 2 months prior to consenting. Patients on 5-alpha reductase inhibitors are allowed on study.

6. Estrogen containing compounds for > 2 months prior to enrollment

7. PC-SPES or PC-x products. Other herbal therapies or supplements will be considered by the Principle Investigator on a case-by-case basis based on their potential for hormonal or anti-cancer therapies.

8. Prior immunotherapy or chemotherapy for prostate cancer

9. Prior radiation therapy to the prostate

10. Prior prostatectomy

11. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

12. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of systemic immunosuppressive therapy within 7 days prior to the first dose of trial treatment, with the exception of steroids for adrenal insufficiency in which case prednisone ≤10mg/day or its equivalent is allowed.

13. Has a known history of active TB (Bacillus Tuberculosis).

14. Hypersensitivity to pembrolizumab or any of its excipients.

15. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

16. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

17. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include carcinoid, basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

18. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroid treatment for at least 14 days prior to the first dose of study treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

19. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

20. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

21. Has an active infection requiring systemic therapy.

22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

23. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

24. Expecting to father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

25. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

26. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

27. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

28. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

4.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 2: Trial Treatments

Study Drugs/Therapies	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Leuprolide (e.g., Lupron, Eligard)[a]	None	22.5 mg[g]	Intramuscular	1st dose at the start of 3 mo ADT run-in[b]. Then 22.5 mg every 3 mo x 3 doses[g] starting Cycle 1 Day 1	N/A
Prednisone (or equivalent medication)[c]	None	Per local standard practice[f]	Oral	Daily for 3 months during ADT run-in[c]. Then daily for 9 months, starting Cycle 1 Day 1	N/A
Abiraterone (e.g. Zytiga, Yonsa)	None	Per local standard practice[f]	Oral	Daily for 3 months during ADT run-in[c]. Then daily for 9 months, starting Cycle 1 Day 1	N/A
Radiotherapy (whole prostate and soft tissue oligometastases)	None	7 Gy x 5 fractions (35 Gy total)	SBRT	1-5 weeks after fiducial marker placement and simulation, over 10-21 days	N/A
Radiotherapy (osseous metastases)	None	10 Gy x 3 fractions (30 Gy total)	SBRT	1-5 weeks after fiducial marker placement and simulation, over 10-21 days	N/A
SD-101[d]	None	5 mg	Intraprostatic, intratumoral	At time of fiducial maker placement (1-5 weeks prior to C1D1) and 1-3 weeks after C1D1 (conjointly prostate biopsies)	N/A
Pembrolizumab (Keytruda)[e]	None for the first dose	200 mg	Intravenous	Day 1 each cycle	21 days

[a]Subjects will receive 3 months of ADT run-in, followed by 9 months of GnRH targeting agent, abiraterone, and prednisone (or equivalent) then discontinuation of ADT. Leuprolide is the preferred GnRH agent, but patients who were already on another GnRH agent may continue this agent. All subjects are required to start or continue abiraterone at enrollment for ADT run-in and subsequent 9 months. Patients who are unable to tolerate or experience toxicity from abiraterone and/or prednisone (equivalent) may discontinue abiraterone and prednisone (or equivalent) and continue on study. GnRH is standard of care treatment and will not be supplied by the study.

[b]Subjects who have received less than 2 months of ADT prior to screening are eligible for the study. For subjects who have been started on Leuprolide or another GnRH agent at time of screening, they will continue the respective GnRH agent for the remainder of ADT run-in (3 months total, accounting for duration of ADT prior to screening). They will continue this GnRH agent for the subsequent 9 months.

[c]Subjects who were not on an antiandrogen, or were on an antiandrogen other than abiraterone at time of screening are required to start or switch to abiraterone (e.g. Zytiga, Yonsa) and prednisone (or equivalent) daily, respectively. They will continue abiraterone and prednisone (or equivalent) daily for the remaining duration of ADT run-in and for 9 months starting on Cycle 1 Day 1. Abiraterone and prednisone (or equivalent) are standard of care treatment and will not be supplied by the study. Prednisone can be increased to 10mg/day if clinically indicated.

[d]SD-101 will be delivered to the dominant prostatic tumor lesion in Arm 2 only. All other study drugs/therapies will be delivered to both Arm 1 and 2.

[e]Severe infusion reactions have been reported in 2 (0.1%) of 1562 subjects receiving pembrolizumab in KEYNOTE-001 and KEYNOTE-002. For severe infusion reactions, stop infusion and permanently discontinue pembrolizumab. Subjects with mild or moderate infusion reactions may continue to receive pembrolizumab with close monitoring; premedications with antipyretic and antihistamine may be considered.

[f]The appropriate dosing of abiraterone and accompanying steroid will be dictated by the prescribed formulation. Generic formulations (e.g. Yonsa) are allowed. Steroid dose can start with QD or BID dosing (e.g. Prednisone 5mg PO QD with Zytiga) and adjusted as indicated clinically.

[g]Equivalent doses of leuprolide are allowed, e.g., 7.5 mg monthly intramuscular doses or 1 mg daily subcutaneous doses, through the 9 month GnRH targeting treatment period. Other GNRH agonists/antagonists that are deemed equivalent can be used.

Trial treatment should begin as close as possible to the date on which treatment is allocated/assigned.

4.2.1 Study drugs – Description, Supply and Storage of Investigational Drugs

4.2.1.1 Pembrolizumab

Pembrolizumab (KEYTRUDA®, MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designated to

block the interaction between PD-1 and its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2).

On September 4, 2014, the United States Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab for treatment of subjects with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The recommended dose of pembrolizumab is 2 mg/kg administered as an IV infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. This indication was approved based on tumor response rate and durability of response. Pembrolizumab is currently being investigated across multiple indications.

Mechanism of Action

Pembrolizumab targets PD-1 on T lymphocytes and prevents interaction with PD-L1 and PD-L2, which are inhibitory receptors expressed on tumor cells and antigen presenting cells. The blockade of PD-1 with PD-L1 and PD-L2 enhances functional activity of the target lymphocyte to facilitate tumor regression and ultimately immune rejection.

Pharmacokinetics and Metabolism

The PK profile of pembrolizumab investigated in Part A of the ongoing study P001 has obtained results following a single dose at 1, 3, and 10 mg/kg pembrolizumab to 17 subjects with solid tumors in Cycle 1. The observed PK profile of pembrolizumab was typical of those observed for other IgG mAbs with a half-life ($t_{1/2}$) of approximately 2 to 3 weeks. There was no indication of dose dependency of $t_{1/2}$ in the 3 dose groups. A dose-related increase in exposure was observed from 1 to 10 mg/kg. The long $t_{1/2}$ supports a dosing interval of every 2 weeks or every 3 weeks.

No traditional metabolism studies were conducted with pembrolizumab per current ICH S6 (R1) guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals. Pembrolizumab has a low potential of eliciting the formation of anti-drug antibodies.

Contraindications

No specific contraindications has been determined for pembrolizumab. Provisional adverse reactions with pembrolizumab are described in the Investigator's Brochure, and exclusion criteria for the study are listed in Section 4.1.3.

Availability

Pembrolizumab will be supplied by Merck Sharp & Dohme Corporation.

Storage and handling

Pembrolizumab is provided as a liquid solution (100 mg/vial) in Type 1 glass vials intended for single use only. The drug product is stored under refrigerated conditions (2 to 8°C). Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours.

Preparation for Administration

Pembrolizumab solution product are a clear to opalescent solutions, essentially free of visible

particles. It is intended for IV administration. The drug can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted MK-3475 solutions in the IV bags. Clinical supplies are to be stored in accordance with specific instructions on the label.

Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

4.2.1.2 SD-101

Classification

SD-101 is a 30-mer phosphorothioate (PS) oligodeoxynucleotide (ODN) enriched with cytidine-phospho-guanosine (CpG) motifs with the following sequence:

5’ – TCG AAC GTT CGA ACG TTC GAA CGT TCG AAT – 3’

SD-101 contains juxtaposed CpG motifs with flanking regions, in a self-complimentary palindromic sequence that is designated as a Class C-type sequence (CpG-C). SD-101 is being developed for an indication in hematologic malignancies, malignant melanoma, and other solid malignancies. No structurally similar compound (i.e. CpG-ODN) has been approved as a drug substance for any indication.

Mechanism of Action

The CpG-C type sequences in SD-101 are an agonist for Toll-like receptor 9 (TLR9) and potent inducers of interferon alpha (IFN-α) production from plasmacytoid dendritic cells (pDCs), as well as pDC maturation and B cell proliferation. TLR9 stimulation by CpG-ODNs may have a significant antitumor effect by several potential mechanisms including enhancement of innate and T-cell immunity, stimulation of cytokines with direct or indirect antitumor activities (including IFN-α), and production of cytotoxic antibodies (Marshall JD et al, 2003; Marshall JD et al, 2005). Signaling by CpG-ODNs through TLR9 requires active uptake of the ODN as TLR9 is present only in specific intracellular compartments (Krieg AM, 2002). The TLR9 signaling occurs in two distinct intracellular structures, early and late endosomes (Honda K et al, 2005; Guiducci C et al, 2006), leading to different outcomes.

Pharmacokinetics and Metabolism
In the healthy normal volunteer trial, 20 subjects (18 years and older) were given a single fixed subcutaneous (SC) dose of SD-101 (0.1, 1.0, 3.0, or 5.0 mg) or placebo, SD-101 levels in the plasma peaked 2 to 4 hours after drug administration. The mean maximum plasma concentration for 6 subjects injected with SD-101 3.0 mg was approximately 7 ng/mL and was higher than for subjects receiving SD-101 1.0 mg. The SD-101 levels in plasma declined after 4 hours. Due to limitations in the analytical method such as a lower limit of quantitation of 5 ng/mL and analyte stability in matrix, the data provided are for information only. The dataset was insufficient for the calculation of parameters such as clearance rate or half-life.

Contraindications
SD-101 should only be administered by routes specified in the protocol. SD-101 should not be administered intravenously. SD-101 is contraindicated for patients who are allergic to any of its components.

Availability
SD-101 will be supplied by **TriSalus Life Sciences**.

Storage and handling
SD-101 contains no preservatives and must be stored under refrigerated conditions (2°C to 8°C). SD-101 is not to be frozen. Vials of SD-101 are for single use only.

Stability
Available stability data indicate that SD-101 (16 mg/mL) is stable for at least 36 months when stored refrigerated at 2 to 8°C, the recommended storage condition.

Preparation for Administration
SD-101 may only be administered by intratumoral injection according to instructions specified in the trial protocol. SD-101 is supplied in single use 2-mL vials containing 0.75 mL of sterile, preservative-free drug at a concentration of 16mg/mL to be diluted with sterile Normal Saline to a total volume of 1 mL. SD-101 will be administered at doses specified in the protocol. Dilutions of SD-101 are to be made at the investigative site using commercially-available sterile Normal Saline, and must be administered within 8 hours of removal of the drug product vial from storage for preparation of the dilution (dosing solution).

Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

4.2.2 Stereotactic Body Radiation Therapy (SBRT)

The goal of SBRT is to deliver ablative radiation therapy while minimizing exposure of surrounding normal tissues. The dose used to treat a given tumor will be based on its location, as normal tissue toxicity is likely to arise from the surrounding organs at risk. The dose level for each metastatic location has been selected based on available evidence and expert consensus.

SBRT should be completed within 3 weeks of the first dose of SBRT. Each site will be treated on an every other day schedule. Not all sites need to receive radiation therapy on the same day.

Radiation therapy will be delivered on specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste, TrueBeam). IGRT is required for this study. Either 3DCRT or IMRT (including VMAT) are all acceptable planning techniques. Planning techniques may differ for each lesion to be treated provided that the tumor motion is properly accounted for with each technique when the target or targets are in or near the thorax region.

4.2.2.1 Dose Specifications

Dose Fractionation

Patients will receive 3 or 5 fractions of radiation as determined by the location of the target to be irradiated. There should be a minimum of 40 hours between treatments for an individual targets. However, a patient may receive radiation for different targets on consecutive days. Maximum dose to 0.1cc of the PTV will be 130% of the prescription dose.

Prescription Doses	
Tumor Location	**Dose**
Primary tumor (prostate, seminal vesicles)	35 Gy (5 fractions)
Soft tissue metastases	35 Gy (5 fractions)
Osseous metastases	30 Gy (3 fractions)

4.2.2.2 Technical Factors

Physical Factors

Only photon (x-ray) beams with photon energies ≧ 6MV will be allowed. For lung metastases, 6 MV photon beam energies are required. For patients with implanted cardiac devices, 6-10 MV photon beam energies are required. FFF photon beams are allowed.

Dose will be calculated using heterogeneity correction algorithms approved by IROC Houston independent of the treatment planning technique. All doses should be reported in terms of dose- to-water and not in terms of dose-to-medium.

Stereotactic Targeting

For the purposes of this protocol, the term 'stereotactic' implies the targeting, planning, and directing of radiation beams along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable 'fiducials.' A fiducial may be external or internal to the patient's body. External fiducials may relate to a frame or treatment device. Internal fiducials may be implanted markers OR reliably identifiable anatomy that is clearly visible on orthogonal kV imaging including the tumor itself. In all cases, the relationship between the fiducial and the actual tumor position in real time should be reliably understood for both planning and treatment.

Isocenter Placement

When using a gantry mounted linear accelerator for this protocol, the isocenter is defined as the common point of gantry, collimator, and couch rotation for the treatment unit. When treating multiple lesions, it is best to use multiple isocenters, each centered on a separate lesion,and to treat different targets on different days in order to decrease treatment time for a single day. For widely spaced lesions (over 10 cm apart), localization is improved when the isocenter is placed in the center of each target and image guidance is performed individually for each target. This is due to the limitation of most IGRT systems which ignore necessary rotational corrections when table shift coordinates are derived. The use of a single isocenter to treat multiple lesions in proximity (<10 cm) is permitted.

Composite Dose Calculations
Composite plans should be generated to incorporate the dose to surrounding normal tissues from each metastasis treated. The composite doses to critical normal tissues will be used to evaluate plan compliance. Composite planning refers to dose summation from multiple treatment sites on a single CT scan that encompasses the relevant anatomy. Composite treatment planning is best accomplished by obtaining a planning CT dataset that incorporate all targets and relevant critical structures in the imaging study. If this is not possible due to restrictions on the size of the imaging study that can be managed by the treatment planning system, CT datasets should be divided into two parts and treatment fields should be adjusted so that dose spillage from the treatment of targets in one dataset to the next is minimal such that the dose contributions do not require summation. The two datasets should be obtained so that they have some amount of overlap that can be used to fuse the information using a rigid registration technique. The use of deformable registration to sum dose is not allowed. In general, it is best to perform CT scanning with the patient in the same position. This implies that, for example, all lesions planned on a gated CT scan must be treated with gating.

4.2.2.3 Localization, Simulation, and Immobilization

Patient Positioning (Immobilization)
Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position throughout treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV). The degree of bladder fullness should be made to duplicate what is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such. Primary tumor treatment with a full bladder is strongly recommended. The use of rectal balloons will be allowed but are not required in this protocol. The use of a rectal balloon will be documented for each patient for future analysis.

Simulation
All patients will undergo CT-based treatment planning in custom made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used) and be adequate to ensure contouring of all targeted lesions, as well as necessary organs at risk (OAR), defined below. High-resolution CT scans should be obtained with uniform slice thickness of ≤ 3mm throughout. If a single CT scan cannot be obtained due to a large spatial separation between metastases (i.e., cervical and femoral metastases), or planning system slice number limitation, multiple CT scans are allowed provided that OAR are entirely encompassed in a single CT scan. CT imaging should be performed so that a composite dose distribution including all treated metastases can be created. Ideally all metastases will be treated in one treatment position. When treating multiple metastases such as a lung and extremity, varying the treatment position may be necessary (i.e. simulation with arms up and arm to the side). Thus, more treatment positions can be used at the discretion of the treating oncologist, but every effort should be made to obtain a composite distributions.

The use of IV contrast is required for liver metastases. For other metastases (central & peripheral lung, cervical/mediastinal, abdominal-pelvic, and spinal/paraspinal), the use of IV contrast is encouraged but will be left to the discretion of the treating physician. The use of other contrast agents is left to the discretion of the treating oncologist. Vascular contrast from the planning dataset is recommended to be converted to water equivalent density if used for planning. Planning datasets without intravenous contrast may be used for dose calculation.

Magnetic Resonance Imaging (MRI)
MRI images are not required for primary tumor SBRT. However, they may be fused for assistance with target and/or normal tissue delineation. MRI images are required for spine SBRT. In patients with no contraindication to gadolinium, axial MRI T1-weighted post-gadolinium and T2-weighted sequences with ≤3 mm cuts, acquired from at least 1 vertebral body above to at least 1 vertebral body below the target lesion(s), are required. MRI T2-weighted sequences alone are permitted in patients with contraindications to gadolinium.

Respiratory Motion Assessment and Management
All metastases with potential for respiratory motion should be evaluated by appropriate means including 4D CT scan, implanted fiducial marker, or flouroscopy at the time of simulation.

Respiratory motion management (RMM) including abdominal compression, active breathing control, breath hold, end expiratory gating, or fiducial marker tracking, is recommended for any metastasis to be treated with motion > 1 cm. A recommended approach would be to use an ITV technique for motion < 1cm, but for motion > 1cm (typically too large for a free breathing ITV) motion management including but not limited to abdominal compression, active-breathing control (ABC), gating, breath hold, etc. should be used.

If a treatment for multiple metastases (i.e., lung and spine) is designed on a CT scan employing motion management (i.e., abdominal compression), all metastases should be treated with the chosen motion management technique in order to generate an accurate composite dose calculation.

Localization Using Daily IGRT
As an SBRT protocol, this study requires the use of IGRT. IGRT is a computer-assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes including rotational changes) to position the treatment beams relative to target regions. Cone-beam CT (CBCT) using a kV imaging head is required for IGRT on this protocol. Use of a shortened CT planning scan for registration may be important for IGRT systems that cannot handle a large number of CT slices. A subset of the planning CT scan can be uploaded to the IGRT system for localization of each targeted lesion. The CT data should include the radiation target of interest plus at least 5cm superiorly and inferiorly.

Patient Preparation for Prostate SBRT
Patients will be advised to adhere to a low gas, low motility diet commencing one day prior to the treatment. Patients will undergo an enema 1-2 hours before simulation and each treatment. If undergoing treatment with a full bladder, patients will drink fluids immediately after the enema and refrain from voiding to achieve a comfortably full bladder.

Treatment Planning/Target Volumes
The definition of volumes will be in accordance with the ICRU Reports #50 and #62: Prescribing, Recording, and Reporting Photon Beam Therapy.

The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT and MR (when available) along with clinical information. The primary tumor GTV (GTVp) for the purposes of this protocol is the whole prostate, or in cases of seminal vesicle invasion the whole prostate and the whole involved seminal vesicle(s), and will also equal the primary tumor Clinical Target Volume (CTVp). The soft tissue oligometastases GTV (GTVstm) is defined as the gross tumor volume of all soft tissue prostate cancer metastases, including lymph nodes, and will also equal the soft tissue metastases Clinical Target Volume (CTVstm). The osseous metastases GTV (GTVom) is defined as the gross tumor volume of all osseous prostate cancer metastases and will also equal the osseous metastases Clinical Target Volume (CTVom) in all cases except spine metastases. CTVom delineation for spine metastases is sextant-based as specified by the International Spine Radiosurgery Consortium Consensus Guidelines (Cox et al, IJROBP 2012).

The Planning Target Volume (PTV) will provide amargin around the CTV to compensate for the variability of treatment set up and organ motion. Primary tumor PTV (PTVp) is defined as CTVp +3-5mm. Soft tissue oligometastases PTV (PTVstm) is defined as CTVstm +3-5mm. Osseous metastases PTV (PTVom) is defined as CTVom +0-2mm. Radiation therapy will be prescribed to the PTV using IMRT, prioritizing normal tissue limits.

4.2.2.4 Critical Structures

Contouring of Normal Tissue Structures
In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. Instructions for the contouring of these organs are as follows:

Spinal Cord
The spinal cord will be contoured based on MRI T2-weighted sequences, ending at L2. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

Cauda Equina
Starting at the conus (end of spinal cord, typically around L1 or L2) include the entire thecal sac into the sacrum

Sacral Plexus
Include the nerve roots from L5 to S3 on each side from the neuroforamina to the coalescing of the nerves at the obturator internus muscle.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.

Brachial Plexus
The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamine on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If PTV of all metastases are more than 10 cm away from the brachial plexus, this structure need not be contoured.

Heart
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

Trachea and Proximal Bronchial Tree
The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree.

- *Proximal Trachea*
  Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV for lung metastases or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

- *Proximal Bronchial Tree*
  The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in Figure 6-1. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation. If there are parts of the proximal bronchial tree that are within GTV, they should be contoured separately, as "proximal bronchial tree GTV", not as part of the "proximal bronchial tree".

Whole Lung
Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

Proximal Bronchial Tree Plus 2 cm
As part of determining if lung metastases are central or peripheral, adhering to the eligibility the zone of the proximal bronchial tree, the SBRT protocols defined an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this structure, the patient is eligible for this protocol. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. This structure is not required by the protocol, but its construction is suggested to facilitate appropriateness of patient selection. Alternately, participating sites may use ruler tools in the treatment planning software to ensure protocol compliance.

Skin
The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Great Vessels
The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

Non-adjacent Wall of a Structure
For the esophagus, trachea and proximal bronchial tree, and great vessels, the nonadjacent wall corresponds to the half circumference of the tubular structure not immediately touching the GTV or PTV, These contours would start and stop superiorly and inferiorly just as with the named structure. The half lumen of the structure should be included in this contour.

Stomach
The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.

Duodenum
The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum.

Bowel (Large/Small)
From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.

Rectum
The entire rectum with contents from the peritoneal reflection of the sigmoid to the anus.

Bladder
The whole bladder should be contoured from bladder neck to the dome.

Urethra
The urethra must be visualized and contoured during the treatment planning process. The institutional standard procedure for this will be followed, which may consist of techniques including MRI fusion, urethrogram, or placement of a urinary catheter.

Kidney (renal cortex)
Both the right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety (the renal cortex)

Liver
The entire liver minus the GTV targets.

Bile ducts
May use the portal vein from its juncture with the splenic vein to its right and left birfurcation in the liver as a surrogate to identify the bile ducts.

Femoral Heads
The ball of the head and socket joint.

Rib
Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow.
Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however,
should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

Other Structures
The constraints tables below contain other structures. These are required if the structure is within 10 cm of the PTV.

Critical Organ Dose-Volume Limits

This primary purpose of this study is to determine the safety of delivering SBRT to multiple targets within one treatment course. To that end composite dose distributions of organs at risk are critical to understand toxicity. Composite dose plans including all treated lesions and organs at risk must be submitted as well as individual SBRT plans to evaluate protocol compliance. To facilitate composite planning, dose to all targets should be calculated on a single CT scan simultaneously with in-plane resolution of at least 2 x 2 x 3mm. If this is not possible, composite plans should be generated incorporating the dose from each metastasis treated. The composite doses to critical normal tissues will be used to evaluate plan compliance.

Dose limits to a point or volume within several critical organs based on the dose fractionation schema (three or five fractions) are assigned based on target tumor location. If a given organ has > 1 Gy dose contribution from both the three and five fraction plans, then the three fraction dose constraints in the table below will be used.

Table 3: OAR Dose Limits for 3 fraction SBRT

Serial Organ	**Volume**	**Volume Dose (Gy)**
Spinal Cord	<0.03 cc	22.5
	<1.2 cc	13
Ipsilateral Brachial Plexus	< 0.03 cc	26
	<3 cc	22
Cauda Equina	<0.03 cc	25.5
	<5 cc	21.9
Sacral Plexus	<0.03 cc	24
	<5 cc	22.5
Trachea and Ipsilateral Bronchus*	<0.03 cc	30
	<5cc	25.8
Esophagus*	<0.03 cc	27
	<5cc	17.7
Heart/Pericardium	<0.03cc	30

Serial Organ	Volume	Volume Dose (Gy)
	<15 cc	24
Great vessels*	<0.03cc	45
	<10 cc	39
Skin	<0.03cc	33
	<10cc	31
Stomach	<0.03cc	30
	<10cc	22.5
Duodenum*	<0.03cc	24
	<10cc	15
Bowel*	<0.03 cc	34.5
	<20cc	24
Rectum*	<0.03 cc	49.5
	<3.5 cc	45
	< 20 cc	27.5
Bladder	0.03cc	33
	<15 cc	16.8
Ureter	<0.03 cc	40
Penile bulb	< 3cc	25
Femoral heads	<10 cc	24
Bile duct	< 0.03 cc	36
Renal hilum/vascular trunk	<15 cc	19.5
Rib	< 0.03 cc	50
	<5 cc	40

Parallel Organ	Volume	Volume Dose (Gy)
Lung (total)	<15% lung volume	20
	< 37% lung volume	11
	1500 cc	10.5
	1000 cc	11.4
Ipsilateral kidney	<130 cc	12.3
Total Kidney	<200cc	15
Liver	<700 cc	17.1

*NOTE: Avoid circumferential irradiation.

Table 4: OAR Dose Limits for 5 fraction SBRT

Serial Organ	Volume	Volume Dose (Gy)
Spinal Cord	<0.03 cc	28
	<0.35 cc	22
	<1.2 cc	15.6
Ipsilateral Brachial Plexus	< 0.03 cc	32
	<3 cc	30
Cauda Equina	<0.03 cc	32
	<5 cc	30
Sacral Plexus	<0.03 cc	32
	<5 cc	30
Trachea and Ipsilateral Bronchus*	<0.03cc	40
	<5cc	32
Esophagus*	<0.03cc	35
	<5 cc	27.5
Heart/Pericardium	<0.03 cc	38

Serial Organ	Volume	Volume Dose (Gy)
	<15 cc	32
Great vessels*	<0.03 cc	53
	<10 cc	47
Skin	< 0.03cc	38.5
	< 10cc	36.5
Stomach	< 0.5cc	35
	< 5cc	26.5
Duodenum*	< 0.5 cc	30
	< 5 cc	18.3
Bowel*	< 0.03 cc	40
	<20 cc	28.5
Rectum*	<0.03 cc	37.45
	<3cc	34.4
	D10%	32.63
	D20%	29
	D50%	18.13
Bladder	< 0.03	37.45
	D10%	18.12
Urethra	<0.03cc	37.45
Ureter	< 0.03 cc	45
Penile Bulb	<0.03 cc	35
	<3cc	19.25
Femoral head	<10 cc	19.25
	1cc	15
Bile Duct	<0.03 cc	41

Serial Organ	Volume	Volume Dose (Gy)
Renal hilum/Vascular Trunk	<15 cc	23
Rib	<0.03 cc	57
	<5 cc	45

Parallel Organ	Volume	Volume Dose (Gy)
Lung (total)	< 37% lung volume	13.5
	< 1500 cc	12.5
	< 1000 cc	13.5
Total Kidney	< 200cc	18
Liver	<700 cc	21

*__NOTE__: Avoid circumferential irradiation.

Rib/Chest wall Dose Constraints
Recent reports have highlighted that the rib and chest wall in proximity to the treated lesion may represent an organ at risk for complication. Tumor location, particularly when located peripherally, will enhance the potential risk for chest wall toxicity. While target coverage should not be compromised to limit dose to the rib/chest wall, every effort should be made to minimize dose to this OAR.

4.2.2.5 Organ at Risk Dosimetry Compliance

Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints. Any dose to spinal cord, cauda equina, sacral plexus above that is listed in Table 3 and Table 4 will be considered an unacceptable deviation. For all other OAR, when OAR dose criteria provided above cannot be accomplished by following planning priorities outlined above, doses to serial OAR of more than 105% of the dose prescribed to the PTV will be scored as unacceptable deviations. Doses to parallel OAR exceeding 110% of the dose prescribed to the PTV will be scored as unacceptable deviations

4.2.2.6 Radiation Therapy Adverse Events

All Radiation Therapy AEs will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Primary Prostate Tumor:
Clinical discretion may be exercised to treat side effects from radiation therapy. Examples of typical medications used in the management of rectal side effects, such as diarrhea, include diphenoxylate or loperamide. Bladder or rectal spasms are usually treated with anticholinergic agents. Bladder irritation may be managed with phenazopyridine. Erectile dysfunction is often treated with medical management or mechanical devices. Proctitis may be treated per standard of care, e.g. steroid foam.

Metastases:
Adverse events related to SBRT for the treatment of metastases are dependent on the location of the metastases treated as well as from exposure of surrounding normal tissues.

For all treated metastases, fatigue is likely to occur and should be transient lasting < 8 weeks. Other adverse events are likely to be related to the specific metastatic location receiving SBRT:

Lung (Central and Peripheral), Mediastinal/Cervical Lymph Node Metastases
Cardiac and Pericardial Injury
Although cardiac and pericardial injury is uncommon in the conventionally fractionated course of RT, with large doses per fraction of SBRT a number of possible side-effects can be seen.

Gastrointestinal/Esophageal Injury
The radiation effects on the esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or longer), or chronic, typically manifesting with dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases.

Central Airway/Bronchial Injury
This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), v5.0.

Lung Injury
Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. Given the small amount of lung that is typically included in the SBRT portals, lung toxicity has not been as dose-limiting as in conventionally fractionated large field RT, but it is nevertheless seen, can be symptomatic, and may be confused with other causes of respiratory deterioration, including infections, and tumor recurrence**.**

Given that larger volumes of lung may be irradiated in this protocol compared to SBRT for primary tumors, it is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Liver/abdominal-pelvic metastases
Very likely (80-90%): Fatigue (which generally goes away after the radiation therapy is completed); skin irritation, redness, itchiness, discomfort; temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

Less likely (30%): Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal track irradiated; gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (<10% permanent changes); chest wall pain, rib fracture (< 10%)

Less likely, but serious (<20%): Radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the Liver; non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease; permanent thrombocytopenia (<1%); this may lead to bleeding; kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

Spinal metastases
Radiation Myelitis
Given the proximity and position of spinal cord in relation to the radiosurgery target, every effort should be made to minimize the radiation dose to the spinal cord. Radiation myelitis is a subacute or chronic clinical syndrome after radiation. The symptoms may include paresthesia,sensory changes, and motor weakness including paralysis. There is no active treatment for radiation myelitis; therefore, it is important to prevent any injury to the spinal cord. Corticosteroids are used when clinical symptoms develop.

Radiation Esophagitis

Patients with thoracic spine treatment will likely develop esophageal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. There are no long-term adverse events reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal esophagus. The consequences of esophageal toxicity, e.g., swallowing difficulty, dysphagia, cough, dehydration, and fistula, should be documented.

Radiation Laryngitis or Pharyngitis
Patients with cervical spine treatment will likely develop laryngopharyngeal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. No long-term laryngopharyngeal toxicity has been reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal larynx and pharynx. The consequences of toxicity, e.g., swallowing difficulty, dysphagia, cough, dysphonia dehydration, and fistula, should be documented.

Tracheal Injury
Although no cases of tracheal injury have been reported with spine radiosurgery, it is prudent to minimize the radiation spillage in the normal trachea. The consequences of tracheobronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should be documented.

Radiation Pneumonitis
There have been no reported cases of symptomatic radiation pneumonitis with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the lung tissue. It is strongly recommended to use radiation beams directed from posterior to avoid passage of radiation through the lungs. Patients with symptoms of pneumonitis will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with non-steroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Compression Fracture of Treated Vertebra
Radiation doses in excess of 19 Gy for a single fraction are associated with higher rates of vertebral body compression (Saghal 2013).

In this protocol, doses per fraction this high are not used, so that the estimated rate of vertebral body compression fracture following spinal metastases treatment should be approximately 10%.

Other Adverse Events
Short-term or long-term injury to the kidney or upper airway has not been reported. If other severe adverse events occur, details should be documented.

Osseous
Erythema, desquamation and alopecia are common side effects from radiation therapy for osseous metastases; other effects are determinate on location of metastasis, and may include pain, edema and neuralgia.

4.2.3 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

4.2.4 Drug Ordering

UCSF will obtain SD-101 directly from **TriSalus Life Sciences**as study supply.

UCSF will obtain pembrolizumab directly from Merck Sharp & Dohme Corporation as study supply.

4.2.5 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

4.2.6 Dose Selection/Modification

4.2.6.1 Dose Selection

The rationale for selection of doses for pembrolizumab and SD-101 to be used in this trial is provided in Section 3.2.2.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

4.2.6.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/ combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care.

For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 5.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to SD-101 intraprostatic injection alone or to pembrolizumab alone, for adverse events listed in Table 5, both interventions must be held according to the criteria in Table 5.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 5.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 5, the combination of [SD-101 intraprostatic injection and pembrolizumab] may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to [the combination or to SD-101 intraprostatic injection alone], re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion .

Table 5: Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab Monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.

4.2.6.3 Dose Modification – SD-101

Adverse events (both non-serious and serious) associated with SD-101 exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

SD-101 must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 6 below.

Table 6: Toxicity Management Guidelines for AEs Associated with SD-101

Adverse event	Management
Dysuria	Check urinalysis and urine culture to rule out urinary tract infection (UTI). Treat UTI with appropriate antibiotics if work-up returns positive. Treat dysuria symptomatically (e.g., Pyridium). If symptoms do not improve or resolve, consider holding further SD-101 therapy or reducing the dose of SD-101 by 50%.
Urinary urgency	**Grade 1:** Monitor closely for clinical worsening. **Grade 2:** Withhold subsequent SD-101 therapies until urinary urgency has resolved to Grade <2. If urgency is grade 1 at time of second SD-101, then SD-101 should be administered at 50% dose.
Hematuria	**Grade 1:** Monitor closely for clinical worsening. Consider lowering the dose of subsequent SD-101 therapies. **Grade 2:** Withhold further SD-101 therapies. Treat symptoms as clinically indicated (e.g. urinary catheter, bladder irrigation indicated). Do not restart SD-101 until hematuria has resolved to Grade ≤1. Treating physicians should discuss with the Medical Monitor prior to any additional SD-101 therapies. If SD-101 is restarted, lower the dose by 50%. **Grade 3 or 4:** Withhold further SD-101 therapies. Treat symptoms as clinically indicated (e.g. transfusion, IV medications, hospitalization, elective endoscopic, radiologic or operative interventions). SD-101 therapy should not resume until hematuria has resolved to Grade ≤1. Treating physicians should discuss with the Medical Monitor prior to any additional SD-101 therapies. If SD-101 is restarted, lower the dose by 50%.
Urinary obstruction	**Grade 1:** Monitor closely for clinical worsening. Consider lowering the dose of subsequent SD-101 therapies. The treating physician has the discretion to place Foley catheter for remaining localized therapies as clinically indicated. **Grade 2:** Withhold further SD-101 therapies. Treat symptoms as clinically indicated (e.g. urethral dilation, urinary or suprapubic catheter). Do not restart SD-101 until urinary obstruction has resolved to Grade≤1. Treating

Adverse event	Management
	physicians should discuss with the Medical Monitor prior to any additional SD-101 therapies. If SD-101 is restarted, lower the dose by 50%. **Grade 3 or 4:** Withhold further SD-101 therapies. Treat symptoms as clinically indicated (e.g. elective radiologic, endoscopic or operative intervention). SD-101 therapy should not resume until urinary obstruction has resolved to Grade ≤1. Treating physicians should discuss with the Medical Monitor prior to any additional SD-101 therapies. If SD-101 is restarted, lower the dose by 50%.

Also, the following dose modification guidelines for SD-101 should be followed:

a. Permanently discontinue SD-101 for treatment-related Grade 4 adverse events of any duration.

b. Hold SD-101 for related Grade 3 adverse events with subsequent dose-reduction of SD-101 to 50% if adverse events return to Grade ≤1 or baseline within two weeks upon restarting SD-101.

c. Dose-reduce or discontinue SD-101 before or concurrently with other treatment regimens such as pembrolizumab, leuprolide, and/or abiraterone if such adverse event(s) is at least possibly related to SD-101.

4.2.6.4 Dose Modification – SBRT

No dose modifications for SBRT are allowed.

4.2.7 Timing of Dose Administration

4.2.7.1 Pembrolizumab

Pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 5.0). Trial treatment may be administered up to 7 days after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

4.2.7.2 SD-101

SD-101 should be delivered intratumorally to the dominant prostatic lesion at a dose of 5 mg per treatment during placement of fiducial marker (1-5 weeks prior to C1D1), and 1-3 weeks after C1D1. SD-101 injection will be administered under ultrasound guidance. Intratumoral injection of 5 mg SD-101 will be performed by the participating radiation oncologist and/or urologist. The second SD-101 injection and prostate core biopsies should be done conjointly, preferably 1-2 weeks after the completion of SBRT to the prostate. For participants in cohort 2, it is permitted to complete the second SD-101 injection and prostate core biopsies while receiving SBRT to oligometastatic sites.

The second SD-101 injection may be delayed up to an additional 14 days for treatment-related toxicity or other reasons per investigator's discretion. Consequently, the prostate core biopsy may be delayed to allow for conjoint occurrence with the SD-101 injection.

All trial treatments will be administered on an outpatient basis with the option of inpatient admission per physician's discretion.

4.2.8 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

4.3 Randomization or Treatment Allocation

Assignment into Cohort 1 (SBRT to ***prostate***) and Cohort 2 (SBRT to ***prostate and oligometastatic sites***) will be determined based on the participant's planned standard of care.

For both cohorts, eligible patients will be randomized 1:1 into Arm 1 consisting of pembrolizumab and RT with intermittent ADT and Arm 2 consisting of pembrolizumab and RT as well as SD-101 with intermittent ADT.

4.4 Stratification

There will be no patient stratification.

4.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 6.2.2.

4.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than pembrolizumab and SD-101
- Radiation therapy not specified in this protocol
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to ameliorate side effects of the abiraterone, or to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

4.6 Rescue Medications & Supportive Care

4.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in greater detail in the Pembrolizumab Investigator's Brochure.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the Pembrolizumab ECI Guidance Document v. 3.0).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the Pembrolizumab ECI Guidance Document v. 3.0, located in Appendix 7.

4.7 Diet/Activity/Other Considerations

4.7.1 Diet

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

4.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

Subjects should agree to use an adequate method of contraception starting prior to the first dose of study therapy through 120 days after the last dose of study therapy, and their partners should be encouraged to use adequate method of contraception as well. The following are considered adequate barrier methods of contraception: condom, spermicide (by the partner), diaphragm (by the partner), copper intrauterine device (by the partner), sponge (by the partner), or spermicide. Appropriate hormonal contraceptives (for the partner) will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study by the subject's partner. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 6.2.6.2. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.7.3 Use in Pregnancy

If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor [redacted] as described here and in Section 6.2.6.2. The site will contact the subject at least monthly and document the subject's partner's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor [redacted] without delay and within 24 hours to the Sponsor and within 2 working days [redacted] if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

4.8 Replacement Policy

All patients who receive any study therapy will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any study therapy may be replaced after discussion with the Sponsor-Investigator. Subjects who have received any dose of study therapy will not be replaced. Patients removed from study for unacceptable pembrolizumab or SD-101 related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to Grade 2 or lower. However, they will not be replaced.

If the treating physician determines that prostate or oligometastatic-directed SBRT can no longer be performed for any reason (e.g., safety concerns), then the participant may continue their participation in their assigned cohort/arm without undergoing prostate or oligometastatic-directed SBRT. Data collected from these participants will be included in the data analysis for their assigned cohort (see section 7.2); they will not be replaced.

4.9 Safety Lead-In

The first 3 patients enrolled into each arm in cohort 1 will be treated and followed for 6 weeks in each arm following initiation of therapy prior to full enrollment onto each arm. If none of the 3 patients experience a DLT, accrual will continue until a total of 21 patients are accrued in each arm. A DLT will be defined as any unacceptable treatment-related toxicity including any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 4 weeks. If at most 1 patient experiences a DLT, 3 additional patients will be accrued; if at most 1 patient experience a DLT, accrual to the respective study arm will continue. If more than 1 patient from either the initial 3-patient safety cohort or subsequent 3-patient safety cohort experiences a DLT, treatment will be halted and the study re-evaluated before continued accrual to the specific arm. In Arm 2, if DLT is attributed to SD-101, the dose of SD-101 will be decreased to 1mg for subsequent enrollment. If the 1 mg dose of SD-101 in combination with radiation therapy and pembrolizumab is not tolerated, the study will be halted and the study re-evaluated before further accrual.

A DLT will be deemed as follows:

a. Any and all adverse events <u>at least possibly</u> related to pembrolizumab, SD-101, and/or radiation shall be included in DLT evaluation
b. Most Grade $\geq$3 AE excluding electrolytes abnormalities with no clinical adverse experiences should be deemed a DLT, except:

i. Grade 3 nausea, vomiting, or diarrhea and grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hrs
ii. Grade 3 fatigue lasting <5 d
iii. Grade 3 HTN that can be controlled with medical therapy

c. AE of episcleritis, uveitis, or iritis of Grade 2 or higher of any duration is a DLT
d. Any toxicity preventing subjects from receiving 75% of abiraterone or 2 doses of pembrolizumab, SD-101, or SBRT during the DLT evaluation period is a DLT.
e. Any toxicity causing greater than 2 weeks of dose delay is a DLT

NOTE: The safety-lead in component reached completion on 11/19/2018 and 04/05/2019 for arms 1 and 2, respectively.

4.10 Interim Analyses and Stopping Rules

A stopping rule for safety will halt accrual to the study and prompt reevaluation of the treatment (e.g. dose, site of intratumoral therapy) if unacceptable treatment-related toxicity (defined as any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 4 weeks) is observed at a frequency of ≥33%. Because of the known excellent safety profile of pembrolizumab, this safety review will occur after 6 patients have been accrued to each arm in cohort 2. Should unacceptable treatment-related toxicity be observed at a frequency of 33% or greater at any time point attributed to SD-101 in Arm 2, SD-101 dose will be lowered to 2mg for subsequent enrollment.

4.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5.0 TRIAL FLOW CHART

5.1 Study Flow Chart

	Screening	Cycle 1 (21-Day)	Cycles 2 to 13 (21-Day)	Treatment Discontinuation	Follow-Up
Assessment Window (Days)	D -42[a]	D1[b]	Day 1 ± 4 Days	≤ 30 Days After Last Dose of Pembrolizumab[c]	Every 12 wks (+/- 2 wks)
Informed consent	x				
Informed consent for future biomedical research	x				
Review of eligibility criteria	x				
Baseline conditions	x				
Medical, surgical, and cancer histories, including demographic information	x				
Baseline medications (taken within 28 days of Day 1)	x				
Concomitant medications		x	x	x	x
Evaluation of clinical symptoms or deterioration			x	x	x
Review adverse events[d]		x	x	x	x
Prostate tumor tissue acquisition or 15 unstained slides[e]	x				
Metastatic tumor tissue biopsy[f]	x			At time of progression	
Prostate core biopsies[g]	At time of SBRT marker placement	1-3 weeks after C1D1			
Treatment administration					
Androgen deprivation therapy (ADT)[h]	3 months prior to C1D1	GnRH targeting agent (leuprolide preferred) + abiraterone + prednisone (or equivalent) for 9 months starting on			

	Screening	Cycle 1 (21-Day)	Cycles 2 to 13 (21-Day)	Treatment Discontinuation	Follow-Up
Assessment Window (Days)	D -42[a]	D1[b]	Day 1 ± 4 Days	≤ 30 Days After Last Dose of Pembrolizumab[c]	Every 12 wks (+/- 2 wks)
		C1D1			
Pembrolizumab (200 mg)[i]		x	x		
SBRT marker placement	1-5 weeks prior to C1D1				
SBRT simulation	1-5 weeks prior to C1D1				
Radiotherapy (SBRT)[j]		x			
Localized therapy with SD101 (Arm 2 only)[k]	At time of SBRT marker placement	1-3 weeks after C1D1			
Clinical procedures					
Physical examination	x	x	x	x	x
Performance status (ECOG)	x	x	x	x	x
Vital signs including Weight[l]	x	x	x	x	x
Disease/tumor assessment[m]	x		x[w,x,y]	x[w,x,y]	x[w,x,y]
Survival and anti-cancer therapy follow-up[n]					x
Laboratory procedures					
Hematology[o]	x	x	x	x	x
Serum chemistry[p]	x	x	x	x	x
Coagulation panel (PT, aPTT, INR)	x			x	
Urinalysis[q]	x		x	x	
TSH, free T3, free T4[r]	x		x	x	x
HIV, HBV, and HCV serology[s]	x				
PSA, testosterone	x	x	x[t]	x[t]	x[t]
Immune monitoring[u]	x	x	x	x	x

	Screening	Cycle 1 (21-Day)	Cycles 2 to 13 (21-Day)	Treatment Discontinuation	Follow-Up
Assessment Window (Days)	D -42[a]	D1[b]	Day 1 ± 4 Days	≤ 30 Days After Last Dose of Pembrolizumab[c]	Every 12 wks (+/- 2 wks)
Imaging procedure					
ECG[v]	x				
Bone imaging[w]	x		x	x	x
Abdominal, pelvis, and chest imaging[x]	x		x	x	x
PSMA PET Image Collection[y]	x				x

anti-HBc = hepatitis B core antigen; HBV = hepatitis B virus, HCV = hepatitis C virus; HIV = human immunodeficiency virus; ECG = electrocardiogram; TSH = thyroid-stimulating hormone; PSA = prostate specific antigen

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

a. Examinations performed as standard of care prior to obtaining informed consent and within 28 days of fiducial marker placement and SBRT simulation may be used rather than repeating tests, and within 60 days of C1D1 for radiographic imaging. For patients who have started on ADT, they must have had imaging prior to initiating hormonal therapy.

b. Perform procedures on cycle 1 day 1 of pembrolizumab unless indicated otherwise.

c. All patients will return within 30 days for a follow up visit, including those who discontinue study therapy early.

d. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

e. Prostate tumor tissue from archival TRUS prostate biopsy must be submitted, if available, in the form of representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (preferred) or at least 15 slides, with an associated pathology report. If archival prostate tissue are unavailable or cannot be obtained, a repeat TRUS prostate biopsy is not required. Sample collection, storage and transportation instructions for samples to UCSF Cancer Immunotherapy Laboratory will be provided in the Laboratory Manual.

f. Patients will undergo an optional metastatic tumor biopsy, if clinically feasible and safe to perform. Biopsy must be collected prior to SD-101 injection and after initiating ADT. Acceptable samples include core needle biopsies of bone or lymph node. At least three cores should be obtained. A fine needle aspirate is not acceptable. Repeat biopsy at time of progression is optional. Sample collection, storage and transportation instructions for samples to UCSF Cancer Immunotherapy Laboratory will be provided in the Laboratory Manual.

g. Mandatory prostatic core biopsies will be obtained 1-5 weeks prior to C1D1 (conjointly with fiducial placement [Arm 1] or with fiducial placement and SD-101 therapy [Arm 2]) and 1-3 weeks after C1D1 (conjointly with the 2nd SD-101 injection for Arm 2). Sample collection, storage and transportation instructions for samples to UCSF Cancer Immunotherapy Laboratory will be provided in the Laboratory Manual.

h. Patients will receive 9 months of GnRH targeting agent, abiraterone, and prednisone (or equivalent) on study starting on Cycle 1 Day 1. Patients are required to receive 9 months of abiraterone (e.g., Zytiga, Yonsa) daily, prednisone (or equivalent) daily and 9 months of GnRH agonist or antagonist that is FDA approved for prostate cancer. Leuprolide 22.5 mg IM every 3 months for 3 doses is preferred, starting on Cycle 1 Day 1. Patients who have received less than 2 months of ADT prior to study enrollment are eligible for this study (See Sections 3.2.2.4 and 4.1). Patients who were on a GnRH agent other than leuprolide may continue the original agent for a duration of 9 months starting on Cycle 1 Day 1. Patients who were on an antiandrogen other than abiraterone prior to study enrollment must switch to abiraterone for 9 months starting on Cycle 1 Day 1.

i. The study treatment pembrolizumab will be delivered IV at dose of 200 mg for a total of 13 cycles or until disease progression, investigator's decision to discontinue treatment, or withdrawal of patient consent. Subjects will start pembrolizumab (C1D1) 1 month after ADT initiation at the earliest, and 4 months after ADT initiation at the latest.

j. Radiotherapy will begin 1-5 weeks after SBRT marker placement, over 10-21 days. Radiotherapy to the whole prostate and soft tissue metastases will be delivered via SBRT at a dose of 7 Gy x 5 fractions (35 Gy total). Radiotherapy to osseous metastases will be delivered via SBRT at a dose of 10 Gy x3 fractions (30 Gy total). Subjects will start SBRT 1 month after ADT initiation at the earliest, and 4 months after ADT initiation at the latest.

k. For Arm 2 only, SD-101 will be delivered to the dominant prostatic lesion at a dose of 5 mg per treatment at the time of SBRT marker placement (1-5 weeks prior to C1D1). A second SD-101 injection will be administered 1-3 weeks after C1D1. See section 4.2.7.2 for details regarding the timing of the SD-101 injections.

l. Vital signs include heart rate, respiratory rate, blood pressures, temperature, weight, and oxygen saturation. Patient should be weighed at the beginning of each cycle. Height should be recorded once during screening or prior to cycle 1 day 1. For first infusion of pembrolizumab, the patient's vital signs should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

m. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure should be used throughout the study for each patient. Available results must be reviewed by the investigator before dosing at the next cycle.

n. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks (3 months) until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first. All patients will be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. Patients will be followed for up to 3 years (years one and two are mandatory; year three is optional).

o. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.

p. Serum chemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin and LDH.

q. Specific gravity, pH, glucose, protein, ketones, and hemoglobin.

r. Thyroid function tests, specifically thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) will be tested during screening, then every 3 cycles after completion of cycle 4 (within 10 days of starting cycle 5, 8 and 11), at treatment discontinuation, and every 12 weeks during follow-up. Further work-up may be needed as clinically indicated.

s. HIV testing to be performed in accordance with national and/or institutional guidelines. Hepatitis B surface antigen, anti-HBc antibody and anti-HBs antibody should be collected during screening. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be collected prior to Cycle 1, Day 1.

t. PSA and testosterone levels will be checked every other cycle (at cycle 1, 3, 5, 7, 9 11, 13), at treatment discontinuation and at follow-up.

u. Sample collection, storage and transportation instructions for samples to UCSF Cancer Immunotherapy Laboratory will be provided in the Laboratory Manual. Screening sample will be collected within 28 days of fiducial placement and/or first SD-101 injection.

v. ECG recordings will be obtained during screening and as clinically indicated at other time points. Patients should be resting and in a supine position prior to ECG collection.

w. Bone imaging (Technetium, bone scan or Sodium-fluoride PET/CT required at screening) will be obtained every 3 cycles after completion of Cycle 4 (within 10 days of starting Cycle 5, 8 and 11), at treatment discontinuation, and every 12 weeks during follow-up in years 1 and 2. In year 3, bone imaging will be obtained if clinically indicated as determined by the treatment physician. If possible, the same scan that was used at baseline should be used for restaging. If both modalities were used at baseline, then the study that demonstrated the highest disease burden should be preferred. Results and disease/tumor assessment will be reviewed by the investigator before proceeding to the next cycle.

x. CT chest, abdomen, pelvis (or MRI when clinically indicated) with contrast will be obtained every 3 cycles after completion of Cycle 4 (within 10 days of starting Cycle 5, 8 and 11), at treatment discontinuation, and every 12 weeks during follow-up in years 1 and 2. In year 3, imaging will be obtained if clinically indicated as determined by the treatment physician. Results and disease/tumor assessment via RECIST v1.1 will be reviewed by the investigator before proceeding to the next cycle.

y. PSMA PET images will be collected for those patients who undergo PSMA PET as part of a separate study. If available, imaging performed within 6 months of C1D1 and at progression will be obtained. PSMA PET scan is not required as part of this study.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart (Section 5.0) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Screening assessments must be performed within 28 days prior to fiducial marker placement (unless otherwise noted). Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of **± 3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor [redacted] for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the

subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

6.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

6.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

6.1.1.6 Assignment of Screening Number

All patients in the screening phase will be assigned a unique screening number for screening log that will be filed on OnCore.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Screening Assessment

The Screening procedures and assessments must be completed within 28 days of SBRT marker placement unless otherwise noted.

- Physical examination
- Vital signs including weight
- Complete medical history and demographic information
- Baseline conditions assessment
- Disease/tumor assessment
- ECOG performance status
- Baseline medications taken within 28 days of Day 1
- Complete blood count (CBC) with differential and platelet count. A manual differential can be done if clinically indicated.
- Blood chemistry assessment, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, fasting glucose, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin and LDH
- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Urinalysis
- Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3)
- HIV testing in accordance with national and/or institutional guidelines

- Hepatitis B surface antigen, anti-HBc antibody and anti-HBs antibody. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be collected prior to Cycle 1, Day 1.
- HCV serology (anti-HCV antibody)
- PSA
- Testosterone
- Blood collection for immune monitoring. Screening sample will be collected within 28 days of fiducial placement and/or first SD-101 injection.
- Review of eligibility criteria
- Informed consent
- Informed consent for future biomedical research
- Prostate tumor tissue acquisition or 15 unstained slides (if archival tissue is available). If archival prostate tissue are unavailable or cannot be obtained, a repeat TRUS prostate biopsy is not required.
- Biopsy of metastatic tumor lesion (if feasible and safe to perform). Acceptable samples include core needle biopsies of bone or lymph node. At least three cores should be obtained. A fine needle aspirate is not acceptable. Subjects have the option of consenting to a repeat biopsy at time of progression. Biopsy must be collected prior to SD-101 injection and after initiating ADT.
- Electrocardiogram (ECG)
- CT chest, abdomen, pelvis (or MRI when clinically indicated) with contrast.*
- Bone imaging (technetium or sodium-fluoride PET/CT).*
- PSMA PET image collection (if available)
    - PSMA PET images will be collected from patients who undergo PSMA PET as part of a separate study. If available, imaging performed within 6 months of C1D1 and at progression will be obtained. PSMA PET is not required as part of this study.

**Note: Radiographic imaging performed as standard of care prior to obtaining informed consent and within 60 days of initiating study treatment may be used to assess oligometastatic disease during screening, rather than repeating scans. For patients who have started on ADT, they must have had imaging prior to initiating hormonal therapy.*

6.1.2.2 SBRT ± SD-101 injection

- SBRT marker placement (1-5 weeks prior to C1D1)
- SBRT simulation (1-5 weeks prior to C1D1)
- Mandatory prostatic core biopsies (at time of SBRT marker placement).
- SD-101 injection (at time of SBRT marker placement, for Arm 2 only).

- Prostate-directed SBRT (cohort 1), or prostate and oligometastasis-directed SBRT (cohort 2): 3-5 treatments to each target over 10-21 days (1-5 weeks after marker placement and simulation). Subjects will start SBRT 1 month after ADT initiation at the earliest, and 4 months after ADT initiation at the latest.

SBRT and associated procedures (e.g., SBRT marker placement/simulation) will be done according to standard of care. See section 4.2.2 for recommended SBRT procedures. Although SBRT will be done according to standard of care, adhering to the recommendations in section 4.2.2 is highly encouraged. The Sponsor-Investigator may need to be notified, as applicable, if SBRT cannot be performed as outlined in section 4.2.2.

If the treating physician determines that prostate or oligometastatic-directed SBRT can no longer be performed for any reason (e.g., safety concerns) following enrollment, then the participant may continue to receive pembrolizumab±SD-101 per their assigned arm without undergoing prostate or oligometastatic-directed SBRT. However, the participant must discontinue the trial if any of the discontinuation criteria are met (see section 6.1.3).

6.1.2.3 Day 1 of all cycles (+/- 4 days for cycles ≥ 2)

- Physical examination
- Vital signs including weight
- ECOG performance status
- Evaluation of adverse events
- Evaluation of clinical response or deterioration
- Concomitant medications
- Complete blood count (CBC) with differential and platelet count. A manual differential can be done if clinically indicated.
- Blood chemistry assessment, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, fasting glucose, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin and LDH
- Urinalysis
- Blood collection for immune monitoring
- Pembrolizumab infusion. Subjects will start pembrolizumab (C1D1) 1 month after ADT initiation at the earliest, and 4 months after ADT initiation at the latest.

6.1.2.4 1-3 weeks after C1D1

- SD-101 injection (Arm 2 only). See section 4.2.7.2 for details regarding the timing of the SD-101 injection.
- Mandatory prostatic core biopsies. For Arm 2, the biopsies should occur conjointly with the SD-101 injection.

6.1.2.5 Cycle 1, Cycle 3, Cycle 5, Cycle 7, Cycle 9, Cycle 11, and Cycle 13

These procedures must be completed within 3 days of starting Cycle 1, Cycle 3, Cycle 5, Cycle 7, Cycle 9, Cycle 11 and Cycle 13.

- PSA
- Testosterone

6.1.2.6 Cycle 5, Cycle 8, Cycle 11

These procedures must be completed within 10 days of starting Cycle 5, 8 and 11.

- Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3)
- CT chest, abdomen, pelvis (or MRI when clinically indicated) with contrast
- Bone imaging (technetium or sodium-fluoride PET/CT). If possible, the same scan that was used at baseline should be used for restaging. If both modalities were used at baseline, then the study that demonstrated the highest disease burden should be preferred.
- Disease/tumor assessment before starting the next cycle.

6.1.3 Withdrawal/Discontinuation

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences as described in Section 4.2.6
- Intercurrent illness that prevents further administration of pembrolizumab or SD-101
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 13 administrations of pembrolizumab.

- Administrative reasons

Following treatment discontinuation, patients will return to the study site for the End of Treatment visit. The End of Treatment procedures are described in Section 6.1.4. Subjects who discontinue for reasons other than progressive disease will have additional post-treatment follow-up visits for disease status. The post-treatment follow-up procedures are described in Section 6.1.5.

6.1.4 End-of-Treatment Study Procedures

To be completed within 30 days of the last dose of study drug.

- Evaluation of clinical response or deterioration
- Physical examination
- Vital signs including weight
- ECOG performance Status
- Evaluation of adverse events

  Note: serious adverse events will be collected for 90 days after the end of treatment as described in Section 6.2.3.
- Concomitant medications
- Complete blood count (CBC) with differential and platelet count. A manual differential can be done if clinically indicated.
- Blood chemistry assessment, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, fasting glucose, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin and LDH
- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Urinalysis
- Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3)
- PSA
- Testosterone
- Blood collection for immune monitoring
- Biopsy of metastatic site at time of progression, if feasible (optional)
- CT chest, abdomen, pelvis (or MRI when clinically indicated) with contrast
- Bone imaging (technetium or sodium-fluoride PET/CT). If possible, the same scan that was used at baseline should be used for restaging. If both modalities were used at baseline, then the study that demonstrated the highest disease burden should be preferred.
- PSMA PET image collection at disease progression (if available)
    - PSMA PET images will be collected from patients who undergo PSMA PET as part of a separate study. If available, imaging performed within 6 months of C1D1 and at progression will be obtained. PSMA PET is not required as part of this study.
- Disease/tumor assessment

6.1.5 Post-treatment/Follow Up Visits

Subjects who complete the treatment period or discontinue early for reasons other than progressive disease will have post-treatment follow-up visits every 12 weeks +/- 2 weeks for up to 3 years (years one and two are mandatory; year three is optional) after completion of therapy, until disease progression, removal from study, or death, whichever occurs first. Subjects will not be followed for overall survival. The following procedures will be performed at the Follow Up Visit(s):

- Record survival and anti-cancer therapy.

  Note: May be collected via telephone calls, patient medical records, and/or clinic visits.
- Evaluation of clinical response or deterioration
- Physical examination
- Vital signs including weight
- ECOG performance Status
- Evaluation of adverse events.

  Note: All treatment related adverse events will be followed until resolution or stabilization to Grade <2.
- Concomitant medications
- Complete blood count (CBC) with differential and platelet count. A manual differential can be done if clinically indicated.
- Blood chemistry assessment, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, fasting glucose, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin and LDH
- Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3)
- PSA
- Testosterone
- Blood collection for immune monitoring
- CT chest, abdomen, pelvis (or MRI when clinically indicated) with contrast
- Bone imaging (technetium or sodium-fluoride PET/CT). If possible, the same scan that was used at baseline should be used for restaging. If both modalities were used at baseline, then the study that demonstrated the highest disease burden should be preferred.
- Disease/tumor assessments

Note: Patients who opt-in to year 3 of follow-up will only require imaging assessments as clinically indicated determined by the treating physician.

6.1.5.1 Blood Collection for correlative studies

Sample collection, storage and transportation instructions for blood samples to UCSF Cancer Immunotherapy Laboratory [redacted] will be provided in the Laboratory Manual.

The time points for immune-monitoring blood sampling are described in the Trial Flow Chart (Section 5.0).

6.2 Assessing and Recording Adverse Events

6.2.1 Definitions of Adverse Events

6.2.1.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

6.2.1.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

6.2.1.3 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

6.2.1.4 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as

anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

6.2.1.5 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

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

6.2.1.6 Life-threatening

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

6.2.2 Recording of an Adverse Event

All Grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v5.0.

If there are specific data plans to this study, such as Grade 1 & 2 AEs are also being entered into OnCore, describe that process here.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0 No AE (or within normal limits)

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

Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

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

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

6.2.3 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved or stabilization. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

6.2.4 Adverse Events Monitoring

All grade 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

[The manufacturer and/or grant sponsor may also need to be notified, as applicable.]

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer to Appendix 5.

6.2.5 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Institutional Review Board (IRB)

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction - A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the treatment or procedure caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the treatment or procedure and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

- Unexpected - An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

  "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of treatment or procedure or as anticipated from the pharmacological properties of the treatment or procedure, but are not specifically mentioned as occurring with the particular treatment or procedure under investigation.

  Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

  Some adverse events are listed in the Investigator's Brochure as occurring with the same class of treatment, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

- Serious - An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
  - Death
  - Life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
  - Congenital anomaly/birth defect

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

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Expedited Reporting to Merck and TriSalus Life Sciences

Refer to sections 6.2.6 and 6.2.7 for details regarding reporting requirements [redacted].

6.2.6 Reporting Events to Merck

6.2.6.1 Pembrolizumab overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. ([redacted]

6.2.6.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following

cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

6.2.6.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

6.2.6.4 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 7 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety [redacted]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local

regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; [redacted]) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

6.2.6.5 Events of Clinical Interest

Selected non-serious and serious adverse events (SAEs) are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to the Merck Global Safety team. (Attn: Worldwide Product Safety; [redacted]).

ECI (both non-serious and serious adverse events) identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to the Merck Global Safety team (Attn: Worldwide Product Safety; [redacted]), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Events of clinical interest for this trial include:

1. An overdose of Merck's product, as defined in Section 6.2.6, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an ALP lab value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

6.2.7 Reporting Events to TriSalus Life Sciences

The Sponsor-Investigator shall notify **TriSalus Life Sciences** of any unexpected fatal and/or life threatening adverse drug reactions associated with the use of SD-101 as soon as possible and no later than seven (7) calendar days after Sponsor's receipt of the information, on an FDA MedWatch or narrative form.

The Sponsor-Investigator shall promptly report all other serious adverse events, regardless of expectedness or causality, to **TriSalus Life Sciences** within 12 calendar days of receipt, and, when necessary, to the FDA and applicable the IRB, according to relevant regulations. The Sponsor-Investigator shall promptly make available such records as **TriSalus Life Sciences** may deem necessary to investigate and/or report an adverse event associated with the use of SD-101 during the study.

E-mail reports to **TriSalus Life Sciences** at safety.reporting@trisaluslifesci.com

6.2.8 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7: Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

Merck product relationship	

6.2.9 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.0 STATISTICAL CONSIDERATION

7.1 Sample size calculation

The sample size calculation for cohort 2 is based on the hypothesis of the study is combination therapy of pembrolizumab with RT with or without SD-101 leads to improved PSA response as defined as the proportion of patients achieving a PSA <nadir + 2 ng/mL at 15 months.

For each arm of cohort 2, the null hypothesis that the true response rate is 0.1% will be tested against a one-sided alternative of 12%, with 16 patients in each arm, we would have 82% of power at alpha of 0.05.

7.2 Statistical Analysis Plan

7.2.1 Analysis population

All patients who receive any part of a dose of RT, SD-101 or pembrolizumab will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any dose of study therapy may be replaced after discussion with the Sponsor-Investigator. Subjects who have received any dose of SD-101 or pembrolizumab will not be replaced.

Only patients in cohort 2, who achieve testosterone recovery to non-castrate levels (>150 ng/dL) at 15 months, will be analyzed for the primary endpoint.

Demographic and baseline characteristics will be summarized by each study arm. In general, frequency distribution and percentage will be used to summarize categorical measurements, while mean with standard deviation and median with range will be used to describe symmetric and skewed continuous measurements, respectively. Univariate analysis among variables will be assessed using the two-sample t-test, Wilcoxon-rank-sum test, Chi-square test, as appropriate. Missing data will not be imputed.

7.2.2 Analysis of Primary Endpoint

After completion of 9 months of GNRH targeting agent, abiraterone, and prednisone (or equivalent), all patients will discontinue ADT to observe for the rate of PSA < nadir + 2 ng/mL at 15 months from the start of radiotherapy and cycle 1, day 1 of pembrolizumab, among patients whose testosterone recovers to non-castrate levels (>150 ng/dL). In standard of care patients with metastatic hormone-sensitive prostate cancer who come off hormonal therapy during intermittent ADT, essentially all patients (>99.99%) will have PSA > nadir + 2 ng/mL at 15 months. The point estimate of the rate of PSA < nadir + 2 ng/mL will be obtained with its 95% confidence interval for participants by arm in cohort 2 and compared to the historical control rate by one-sample binomial test.

Safety and tolerability
Adverse events occurring on study will be summarized for all participants that received study intervention (including pembrolizumab, SD-101, SBRT to prostate, SBRT to oligometastatic sites) by maximum toxicity grade for each study arm. The toxicity grade for laboratory data will be calculated using CTCAE v5.0 and the lab data will be summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy. All treatment related adverse events will be graded using NCI CTCAE v5.0 and will be recorded and listed.

7.2.3 Analysis of Secondary Endpoints

Testosterone-PSA Uncoupling
Testosterone-PSA uncoupling is defined as PSA < 50% baseline and < 20ng/mL for at least 3 months after testosterone recovers to >150 ng/dL. In patients with metastatic hormone-sensitive prostate cancer off hormonal therapy, >90% patients are expected to have PSA increase to > 50% baseline after 3 months of testosterone recovery. Therefore, the presence of PSA-testosterone uncoupling in this study may serve as a surrogate of immunotherapeutic responses induced by pembrolizumab combined with RT (arm 1), or RT with SD-101 (arm 2), if a prolonged PSA < nadir + 2 ng/mL is not achieved. The point estimate of testosterone-PSA uncoupling rate will be obtained with its 95% confidence interval for each arm in cohort 2.

Time to Clinical Progression
The time to clinical progression in each study arm in cohort 2 is defined as the time to radiographic progression by PCWG-2 criteria (Scher HI et al, 2008), time to symptomatic progressive disease, or PSA progression, whichever comes the first. Kaplan-Meier estimate will be obtained for the time to clinical progression in each study arm in cohort 2.

Progression-Free Survival
Progression-free survival (PFS) will be estimated for each study arm on cohort 2 by Kaplan-Meier estimate, where PFS is a composite endpoint based on PSA progression, radiological progression, clinical deterioration, or death.

7.2.4 Analysis of Exploratory Endpoints

Immunohistochemistry (immune cell subsets and PD-L1)
For all subjects, immune cell subsets localization and PD-L1 staining will be assessed by immunohistochemistry in tumor biopsies and will be summarized by descriptive statistics Immunohistochemistry will be performed in the UCSF Cancer Immunotherapy Laboratory per established SOPs. Based on prior experience tissue will be designated into 3 distinct compartments: benign epithelium, tumor centers, and tumor interfaces. Tumor interfaces will be defined as fields where malignant and benign epithelium are present. Automatic cell counts for single- and double-stained cells will be determined for each field with color-specific algorithms. The cell count for each compartment will be reported as the mean for each of the five quantitated fields. Cells of interest will include CD3+ T cells, CD3+ Ki67+ proliferative T cells, CD4+ FoxP3- helper T cells, CD4+ FoxP3+ regulatory T cells, CD8+ cytotoxic T cells, as well as PD-1 expression on the different lymphocytes. Tumors will be categorized based on the frequency of tumor cells or of immune cells staining positively for PD-L1 as follows: IHC 0: <1%, IHC 1: 1-<5%, IHC 2: 5-<10% and IHC 3: >10%. Frequency distribution and percentage will be used to

summarize PD-L1 expression by at baseline and at time of progression. For patients who undergo a repeat biopsy of metastatic lesion, changes in immune cell infiltration and PD-L1 expression will be summarized using descriptive statistics.

Gene signature biomarker

To identify individual genes whose expression levels at baseline are associated with testosterone-PSA uncoupling, we will apply two-sample Wilcoxon tests to compare patients who achieve uncoupling and those who do not for each arm. Adjusted P values controlling for false discovery rate (Benjamini and Hochberg method) will be derived. In addition, to assess association of baseline immune gene signature with uncoupling, the median expression level of the component genes will be used to represent the signature and two-sample Wilcoxon tests will be used. For genes or signatures that emerge as significantly associated with response, logistic regression models will be used to assess their independent association with response after adjusting for known clinical prognostic factors. Association of gene expression levels at baseline and PFS will be explored using the Cox proportional hazards regression model. Hierarchical clustering superimposed with response status, relevant baseline or prognostic characteristics or experimental factors will be performed using Spearman correlation and complete linkage to visualize the discriminating power of the immune gene expression and the correlative structure among the genes and the samples.

Circulating immune cell subsets

For both cohorts, flow cytometry of circulating immune cell subsets will be performed on baseline (before starting any study therapy), on-treatment (while receiving RT with or without SD-101 and during cycle 1-13 pembrolizumab), and post-treatment (after completing all cycles of pembrolizumab and during follow-up) PBMC. Established flow cytometry panels will examine B cell and T cell populations. Immune cell quantification will be summarized by changes from baseline, on-, to post-treatment using descriptive statistics. Furthermore, paired Wilcoxon signed-rank test will be applied to test the pre-on, and on-post treatment changes. When available, immune cells digested from resected tumor tissues will also be assessed by flow cytometry.

TCR repertoire

For both cohorts, the change in circulating and tumor-infiltrating TCR from baseline (before starting any study therapy), on-treatment (while receiving RT with or without SD-101 and cycle 1-13 pembrolizumab), and post-treatment (after completing all cycles of pembrolizumab and during follow-up) will be assessed by calculating the number of unique clonotypes, read depth and Shannon diversity index. Repertoire overlap and change between sequencing experiments will be measured using Baroni-Urbani and Buser overlap index and Morisita's distance, respectively. TCR repertoire analysis will be performed by the UCSF Cancer Immunotherapy Laboratory.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 8.

Table 8: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection
SD-101 10 mg/ 2 mL or 100 mg/ 2 mL	Solution for injection

8.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

8.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

See Section 4.2.1 for details on the storage and handling of pembrolizumab and SD-101.

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF Institutional Review Board (IRB). Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and any participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 5 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

9.8 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.9 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Institutional Review Board (IRB). Prior to implementing this protocol at any participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before any participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

9.10 Protection of Human Subjects

9.10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

9.10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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11.0 APPENDICES

Appendix 1 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 2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

*As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Appendix 4 Data and Safety Monitoring Plan for Phase II Trial with Safety Lead-In

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of all participant data in safety lead-in phase
- Approval to enroll past safety lead-in phase by DSMC Chair or Vice Chair
- Semiannual auditing after safety lead-in phase
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II studies with a lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment afterwards. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial.

After the completion of enrollment in the safety lead-in phase, the Principal Investigator will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the study. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited semiannually, with a random selection of twenty percent of the participants reviewed (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. The assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. Additionally, a regulatory audit will occur on a biennial basis to review all regulatory documents for the trial.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – The adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center's Site Committee. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, All SAEs are reviewed and monitored by the DSMC on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If an SAE involves death, and occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s), and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, then the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator is responsible for notifying the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator's Brochure or package insert.

If at any time the Principal Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and DSMC Director must be notified within one business day.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]

John McAdams (DSMC Director)
[redacted]

Appendix 5 Specimen and blood collection

A. For tissue analysis:

Sample collection, storage and transportation instructions for samples to UCSF Cancer Immunotherapy Laboratory will be provided in the Laboratory Manual.

B: For blood analyses:

Sample collection, storage and transportation instructions for samples to UCSF Cancer Immunotherapy Laboratory will be provided in the Laboratory Manual.

Appendix 6 Prohibitive Medication

Medications to Avoid
CC# 16703: Phase 2 Trial Pembrolizumab or Pembrolizumab in Combination with Intratumoral SD-101 Therapy in Patients with Hormone-Naïve Oligometastatic Prostate Cancer Receiving Definitive Prostatic Radiation and Intermittent Androgen Deprivation Therapy

The following is a list of medications to avoid while you are participating in this study. If you go to any medical visit, please take this list with you for the doctor's reference.

Before you begin treatment, Dr. Oh or one of his associates will review all medications you are taking. Make sure you talk with Dr. Oh before you start or stop taking any medications. This list contains only the most common drugs that are known to interact with the drugs used in this study. It is very important to discuss all medications that you are taking with your study doctor. This information will be reviewed at each study visit.

Generic Name	**Brand Names ®**	**Generic Name**	**Brand Names ®**
Eulexin	Flutamide	Goserelin	Zoladex
Bicalutamide	Casodex	Nilandron	Nilutamide
Cabazitaxel	Jevtana	Nizoral	Ketoconazole (systemic)
Diethylstilbestrol		PC-SPES (or any other PC-X product)	
Docetaxel	Taxotere	Radium-223	Xofigo
Enzalutamide	Xtandi	Sipuleucel-T	Provenge