Official Title: Phase II Trial of Sipuleucel-T and Stereotactic Ablative Body Radiation (SABR) for Patients with metastatic castrate-resistant Prostate Cancer (mCRPC)

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Phase II Trial of Sipuleucel-T and Stereotactic Ablative Body Radiation (SABR) for Patients with metastatic castrate-resistant Prostate Cancer (mCRPC)

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version # 13

PROTOCOL NUMBER: STU 102012-026
PROTOCOL TITLE: Phase II Trial of Sipuleucel-T and Stereotactic Ablative Body Radiation (SABR) for Patients with metastatic castrate-resistant Prostate Cancer (mCRPC)

Principal Investigator (PI) Name: **Raquibul Hannan, MD, PhD**

PI Signature: _____

Date:_____

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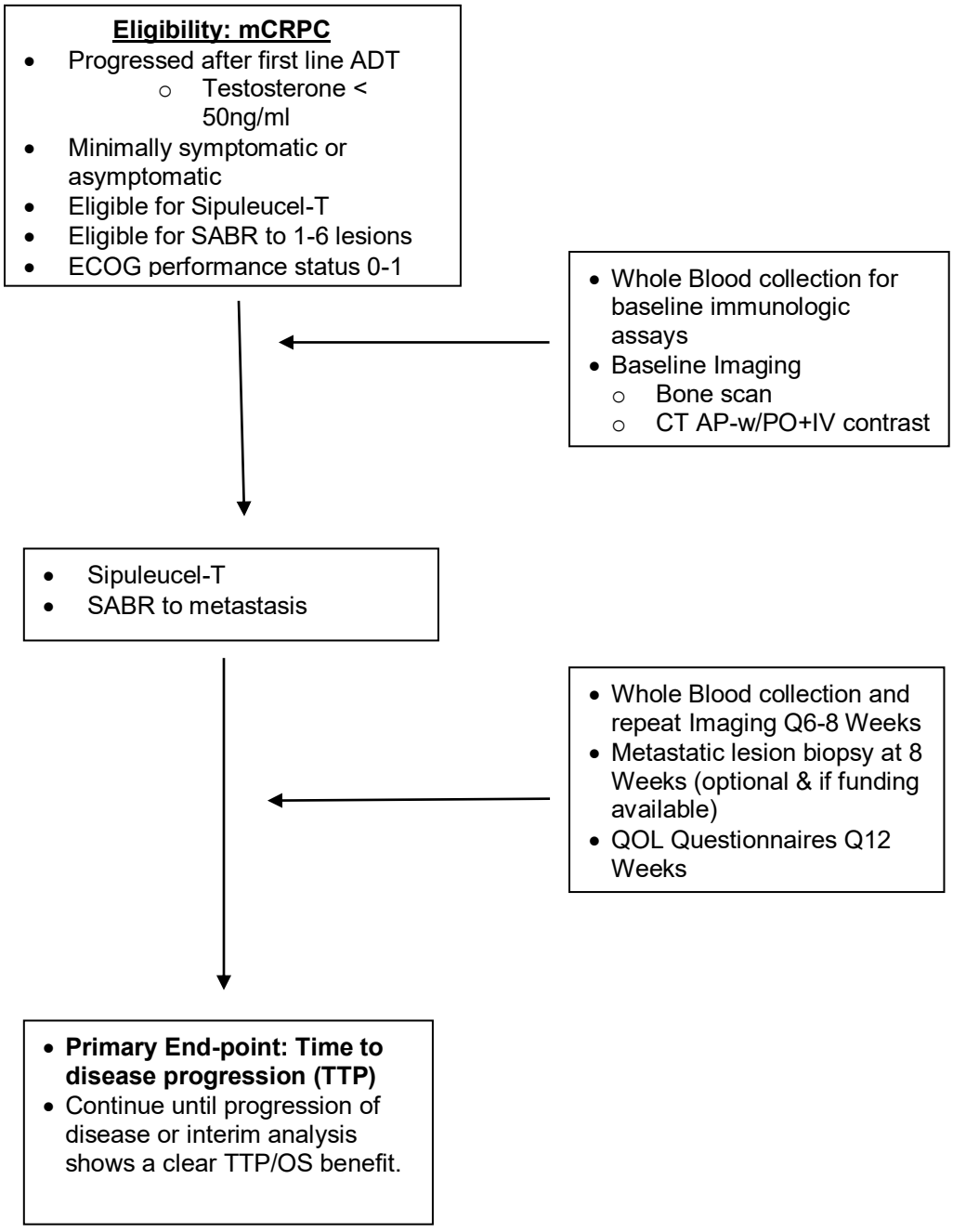
LIST OF ABBREVIATIONS

ADT	Androgen depravation therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
bPFS	Biochemical progression Free Survival
BPI	Brief Pain Inventory
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FACS	Florescence Activated Cell Sorting
H&P	History & Physical Exam
HRQOL	Health-related Quality of Life
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IV (or iv)	Intravenously
mCRPC	Metastatic Castrate Resistant Prostate Cancer
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PAP	Prostate acid phosphatase
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
PCaSS	Prostate Cancer Specific Survival
PSA	Prostate-Specific Antigen
QL	Quality of Life
RT	Room Temperature
SABR	Stereotactic Ablative Body Radiation
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable Disease

WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Phase II Trial of Sipuleucel-T and Stereotactic Ablative Body Radiation (SABR) for Patients with metastatic castrate-resistant Prostate Cancer (mCRPC)
Short Title	Combination therapy of Sipuleucel-T and SBRT for mCRPC
Protocol Number	STU 102012-026
Phase	Phase 2
Methodology	Single arm, open label.
Study Duration	Ten years (seven years for enrollment and 3 years for follow-up).
Study Center(s)	Multi-center
Objectives	To evaluate the improvement in time to progression (TTP) of disease in mCRPC after concurrent treatment with Sipuleucel-T and SABR
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	mCRPC patients, asymptomatic or minimally symptomatic with ECOG 0,1.
Study Product(s), Dose, Route, Regimen	Sipuleucel-T (brand name Provenge)—IV infusion; SABR dose varying from 21Gy-33Gy in 1-3 fractions.
Duration of administration	Six Weeks.
Reference therapy	Sipuleucel-T treatment alone (Published Data—historic control)
Statistical Methodology	The Kaplan-Meier method with the 95% confidence interval will be used to evaluate the primary endpoint of TTP and one-sample log-rank test will be used to compare this with the published value.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Prostate cancer is the most prevalent cancer among men in the U.S with an estimated incidence of 241,740 and deaths of 28,170 in 2012 (SEER). While there are many effective treatment options for localized prostate cancer, the outlook for metastatic disease remains grim with limited effective treatment option. The five-year relative survival for localized disease is 100% whereas that for metastatic disease is 27.8% (SEER). Therefore, there remains a great need for improvement in the therapeutic management of metastatic prostate cancer.

1.2 Stereotactic Ablative Body Radiation (SABR)

Stereotactic ablative body radiation (SABR) is an emerging treatment paradigm defined in the American Society of Therapeutic Radiology and Oncology guidelines as a "treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body" [1] . Potential indications for SABR include a broad spectrum of tumor types and locations.

Previous studies have demonstrated multiple immunogenic properties of radiation therapy, especially when given at high doses such as with SABR [2, 3]. Since SABR is a highly focused therapy, it does not inherently immunocompromise the host. By not surgically removing the tumor, the body retains the antigen depot (dying tumor cells) within the host. Furthermore, since SABR causes local inflammation, dendritic cells (DCs) are attracted into the tumor. These DCs rapidly take up tumor antigens and traffic to regional lymph nodes; during this process they are activated. Once in the cortex of the lymph node, tumor antigens on DCs are efficiently presented by cell surface Class I MHC molecules to T cells. Interestingly, radiation causes a dose-dependent increase in MHC I tumor neo-antigen presentation to tumor cells [4]. The T cells initiate an adaptive immune response resulting in antibody production and the expansion of cytotoxic T cells. These are delivered to both the primary and metastatic tumor sites. There is also evidence from both pre-clinical and clinical studies that radiation therapy, specifically at ablative doses typical of SABR, initiates and augments an immune response by altering the tumor microenvironment. In a pre-clinical rodent syngeneic model, this was demonstrated for prostate cancer using a Listeria-PSA vaccine by Hannan et. al [5]. In the clinic, this was shown recently by Postow et. al. who demonstrated that the abscopal effect (whereby SABR delivered to a primary site of cancer resulted in a complete response at metastatic sites) was due to an increase in tumor-specific T-lymphocytes and a decrease in MDSC and other immune regulatory cells following the combination treatment of SABR and CTLA-4 immunotherapy [6]. A phase I trial was recently published for metastatic melanoma and renal cell cancer where HD IL-2 was combined with SABR with encouraging results [7].

1.3 Sipuleucel-T

Sipuleucel-T (Provenge) is a therapeutic cancer vaccine consisting of autologous infusion of dendritic cells that are activated by *ex vivo* treatment with prostate acid phosphatase (PAP) and a GM-CSF fusion protein, PA2024. Sipuleucel-T has demonstrated approximately 4 months of overall survival (OS) benefit in mCRPC patients in three phase III randomized trials and is currently FDA approved for this stage of prostate cancer patients[8-10]. The D9901 trial enrolled 127 patients with asymptomatic mCRPC. The median survival time for patients treated with sipuleucel-T was 25.9 months comparing to 21.4 months for placebo-treated patients (P=0.01) [9]. A similarly designed trial, the IMPACT trial enrolled 512 mCRPC patients and the median survival time for sipuleucel-T patients was 25.8 months comparing to 21.7 months for placebo-treated patients (P=0.032)[10]. Both of the trials allowed crossover of patients and therefore

taking crossover into account, the predicted survival benefit is reported to be approximately seven months.

Administration of sipuluecel-T consists of leukapheresis of the patient's own blood to collect WBC consisting of DC. This is followed by activating of the DC by PA2024. Three to four days later this product is infused back to the patient. This process is repeated a total of three times two weeks apart. The side effects of sipuleucel-T are mostly limited to chills, fever, fatigue, nausea and headache which usually occur within the first few days of infusion. In addition, more serious cardiovascular events were observed at a rate of 2.4% vs 1.8%, cerebrovascular events of 3.5% vs 2.6% and cord compression of 1.7% vs 0.3% in patients treated with sipuleucel-T and placebo respectively.

1.4 Rationale

As applied in concert with sipuleucel-T in the present study, SABR is intended not only as a systemic cytoreductive agent but also an immunostimulant. In the Norton-Simon hypothesis of malignant tumor progression, tumor growth can be plotted on a curve that very closely resembles the Gompertz model of human population growth [11]. One notable difference, however, is that instead of reaching a steady-state level, as would be the case for a society's population, relentless tumor growth will tend to continue steadily to the point of lethality for the host once the systemic disease burden reaches an overwhelming level. By aggressively cytoreducing the tumor burden at the outset of sipuleucel-T treatment, in addition to maintaining the burden of death below the lethal threshold, the growth dynamics may be altered to render the remaining cells more susceptible to the immunotherapy. Therefore, the purpose of SABR would be two fold. It would irradiate sites of disease that are bulky and resistant to systemic agents, and can eventually serve as origins of further tumor spread and metastasis. Simultaneously, SABR would act as an *in-situ* tumor vaccination by initiating antigen presentation and immunocyte infiltration, thereby acting synergistically with sipuleucel-T in facilitating an effective immune response and eventually affecting disease progression, quality of life and overall survival.

Metastatic prostate cancer can be seen as composed of bulky sites of disease and innumerable micrometastatic disease sites that are below the resolution limit of radiographic imaging. Systemic therapies like hormonal therapy or chemotherapy alone, which are effective towards micrometastatic disease but less so to the bulky sites of metastasis, can result in response, but ultimately the tumors progress resulting in declining quality of life and death from cancer. Historically, the use of local therapies such as surgical metastectomy or conventional radiation for a purpose other than palliation was ineffective since the tumor distribution was systemic. However, there is growing evidence that this new, potent, highly focused, and convenient form of radiation called SABR can dramatically debulk and even eradicate bulky tumor deposits [12-15]. Importantly, since SABR is shown to be immunostimulatory, and immunotherapy has radiosensitizing properties, the combination of the two is expected to be synergistic [2]. In addition to the initiation of antigen presentation by SABR, tumor irradiation will actively recruit DCs into the tumor and to the draining lymph nodes by the release of danger-associated molecular patterns (DAMPs) that are activated by sipuleucel-T, as shown by pre-clinical studies [16, 17]. Therefore a combination treatment that offers eradication of the bulky progressive sites and simultaneously synergizes with the concurrent systemic treatment of immunotherapy to eliminate the micrometastatic disease is expected to improve outcome dramatically and even offer cure to this group of patients that currently only receives palliative treatment.

Therefore, we propose a single-arm, open-label, phase II trial of sipuleucel-T and SABR administered concurrently. The safety profiles of both SABR and sipuleucel-T are excellent and therefore there are limited concerns for toxicity when they are administered concurrently. Given the three randomized phase III clinical trials of sipuleucel-T available for comparison as historic control, a two-arm trial is not necessary.

The primary end point of this study is to measure improvement in time to progression (TTP) of metastatic prostate cancer compared to the reported TTP of 14.6 weeks with treatment with sipuleucel-T alone [10]. A significant improvement on the historically reported values of TTP would justify seeking a phase three trial to show the efficacy of this regimen in improving overall survival. One of the secondary endpoints will be augmentation of the immune response. An immune response in this case would constitute results of two immunologic assays and also a radiographic response to non-target sites. Additional secondary endpoints of this trial will be those that are recommended by the Prostate Cancer Working Group and typically assessed in a phase III trial of prostate cancer and include progression free survival (PFS), biochemical progression free survival (bPFS), prostate cancer-specific survival (PCaSS), overall survival (OS), improvements in quality of life (QOL) and cost effectiveness analysis.

1.5 Correlative Studies

The correlative studies will explore the mechanisms of possible immune enhancement by SABR. Activation of each arm of the immune response will be evaluated separately utilizing different assays. The humeral response will be evaluated using ELISA to measure the titer of tumor-specific antibodies generated by SABR and sipuleucel-T against not only PAP and PA2024, but also an array of known prostate cancer antigens [18]. An overall increase in tumor antigen-specific antibody will be measured using immunoblotting with patient sera as a source of primary antibody [19].

Enhancements of increased cytotoxicity to prostate cancer cells can be measured by cytotoxicity assays. Antibody-dependent cell-mediated cytotoxicity (ADCC) measures the cell-killing ability of certain lymphocytes that require the target cell to be marked by an antibody and thus measures the humeral response [20]. On the other hand, lymphocyte-mediated cytotoxicity assay will measure the formation of tumor-specific CTLs among the lymphocytes collected from patients with the controls being lymphocytes collected from the same patients before SABR and before sipuleucel-T. Since it is not practical or feasible to obtain sufficient quantities of tumor cells from each patients to assess a quantitative cytotoxicity by these assays, established allogenic human prostate cancer cell lines LNCaP and PC3 will be used for this purpose. It is a generally accepted principle of tumor immunology that there will be many common tumor antigens between different patient tumors of same site origin, and therefore tumor cell lines as well [20]. In fact, the tumor antigens (PSA, CEA, CA 19-9 etc.) that are in clinical practice are reported to be present in a significant portions of patients of the respective tumor site. This concept of commonality of tumor antigens between allogenic tumor cell lines and patients is put into clinical practice by the GVAX anti-tumor vaccine which is currently in early phase clinical trials for pancreatic, melanoma and prostate cancer [21, 22]. GVAX consists of multiple human tumor cell lines of the respective site, that is modified to express GM-CSF, and killed with radiation prior to injection in patients. The presence of common tumor antigens in the cell lines and patient's tumors, leads to induction of an immune response. The LNCaP and PC-3 cell lines has been shown to express many of the common prostate cancer antigens, and therefore, is an appropriate surrogate to be used instead of patient's own cells and has been used in similar *in vitro* cytotoxicity assays [23-27].

Cytokines are hormonal messengers responsible for most of the effects in the immune system such as activation of innate versus adaptive immune response, cellular versus humeral immune response [28, 29]. For example, an increased level of IL-2 and IFN-γ suggests activation of Th1 cells leading to activation of macrophages and suggests a cell-mediated adaptive immune response whereas IL-4 and IL-5 may indicate Th2 activation and induction of humoral immunity [20, 29]. An increase in IL-17 may suggest activation of autoimmune responses [30]. Therefore, measurements of serum cytokine levels have generally been used previously in clinical trials as surrogates to assess specific activation of immune pathways [31, 32]. Serum cytokines from this clinical trial before and after SABR will be measured using an extensive array of cytokines to explore the specific immune pathways that are initiated by SABR. The planned array of cytokines will measure levels of the following cytokines before and after treatment for each patients: Th1/Th2/Th17 cytokines: IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, IL-17 TNF-α; pro-inflammatory cytokines: GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α;

Chemokines: Eotaxin, MIP-1β, TARC, IP-10, IL-8, MCP-1, MCP-4, KC, and others including IL-6, IL-12, TGF-β and HMGB1.

Many surrogate markers for activated and proliferating lymphocytes have been described. Some of these markers include CD25, CD71, CD45RO, CD107a, CD54, CD69, Ki67 and ICOS/CD278 [33-36]. These markers are easily measured with antibodies specific for the markers that are tagged with a fluorophore utilizing FACS analysis. These measurements from PBMCs collected from patients before and after treatment will give us further information regarding the intensity of the immune response.

The relative levels of different monocyte subpopulations in the tumor biopsy sample after treatment as well as in the peripheral circulation often dictate the overall outcome of an immune response, and has been reported in previous immunotherapy trials [7]. Exploration of possible mechanisms of treatment failure can be explored from this analysis as well. Therefore the following subpopulation of cells will be quantified in patient PBMCs (and in tumor biopsy samples where applicable) collected before and after treatment utilizing some of the listed markers specific for those cells:

Immune Cells	**Markers**
Lymphocytes	
Cytotoxic T Lympocyte (CTL)	CD3, CD8
NK	CD3-, CD8, CD16, CD56, CD11b
NKT	CD3, CD16, CD1d
Helper T Cells	CD3, CD4
Th1	IL-18 receptor α, CXCR3, T cell Ig domain, TIM-3, T-bet
Th2	T1/ST2, TIM-1, TIM-2, GATA-3
Th17	Unknown, differentiated by IL-17 production, ROR-γT
T_{reg}	CD4+CD25+FoxP3+
Memory T Cells	CD45RO
T_{CM}	CD4/CD8, CD62L, CCR7
T_{EM}	CD4/CD8, CCR7−, CD45RA−, CD27
B Cells	CD19, mIg, FcR, CR, CD3-, HLA-DR
MDSC	CD14+, CD11b, CD33, CD 15, CD4, CD8-, HLA-DR-/low
Neutrophils	FcR, CR-,CD3-, HLA-DR-, GR-1^{+high}, CD11b, Ly6G
Macrophages	FcR, CR, HLA-DR, GR-1^{+mid}
DC	
Myeloid DC-1	CD11c, TLR2,TLR4
Myeloid DC-2	CD 141, TLR2,TLR4
Plasacytoid DC	CD303, TLR7,TLR9

Table 1: PBMC subpopulations and their markers.

1.6 Health-related Quality of Life (HRQOL) and Economic Analysis

In the United States, total national health expenditures (NHE) increased from $7.14 billion in 1990 to $2.23 trillion in 2007, which represents an average annual growth rate of 7.0%. In contrast, over the same period, U.S. gross domestic product (GDP) increased from $5.8 trillion in 1990 to $13.8 trillion, or average 5.2% annual growth rate. Given that national health expenditures have grown faster than GDP, the share of GDP devoted to health expenditures has increased from 12.3% in 1990 to 16.2% in 2007[37]. Moreover, national health expenditure growth is expected to continue to outpace income growth, with total NHE reaching $4.35 trillion by 2018, accounting for 20.3% of GDP (CMS 2009). There is growing concern that these trends in health expenditures are not sustainable. For the Medicare program, current estimates of the present value of total unfunded

liabilities through the year 2083 (the present value of the difference between projected future Medicare expenditures and Medicare revenues over the next 75 years under current Medicare policy) total $89 trillion, with Medicare's Hospital Insurance ("Part A") trust fund projected to be depleted by 2017[38].

Prior studies have estimated that about half of the recent growth in health expenditures is attributable to advances in various forms of health technology, including new pharmaceutical products, surgical procedures, imaging modalities, and new biomarkers[38]. While almost all of these new technologies offer some potential to improve clinical outcomes, they also more often than not add to health expenditures. Within the context of unsustainable trends in health expenditures, a key policy question relates to whether the extent of improvement in outcomes associated with the use of a new technology is attained at a "reasonable" additional cost, compared to existing technology. Indeed, the value offered by new technologies is being subjected to increasing scrutiny by reimbursement authorities in many health systems worldwide. For example, in the United Kingdom, the National Health Service bases payment policy decisions for new technologies on recommendations from the National Institute for Health and Clinical Excellence (NICE), which in turn are substantially influenced by cost-effectiveness analysis yielding an estimated additional "cost per quality-adjusted life-year (QALY) gained" via use of the new technology. Currently, NICE usually considers technologies offering improved outcomes at a cost less than £20,000 to £30,000 per QALY gained (about $33,000 - $50,000) acceptable, though exceptions are common[39].

The American Cancer Society estimates 241,740 newly diagnosed prostate cancer patients with 28,174 prostate cancer related deaths in 2012 [40]. The NIH estimates that the overall direct cost of cancer in the United States in 2010 was $102.8 billion with prostate cancer being the fifth most costly cancer accounting for over $12 billion in annual cost in 2010 and $19 billion projected in 2020 [40, 41]. The rapidly increasing costs of prostate cancer treatment, driven by a combination of advanced surgical, radiation, and pharmaceutical treatment technologies, have catalyzed increased scrutiny regarding current treatment approaches for prostate cancer [42-44]. In fact, prostate cancer has been described as the litmus test for healthcare spending reform efforts [45]. With several recent novel therapeutics recently approved in the management of castration-resistant prostate cancer, the economic implication of therapeutic modalities for men with mCRPC is certainly applicable to this protocol and thus will be studied in a correlative approach [46-48].

Therefore, we propose to evaluate the cost effectiveness of the combined treatment and assess patients' health related quality of life, in order to evaluate the economical consequence of using the two new technologies proposed in this study and its impact on quality of life. Based on the primary hypothesis of this study that time to progression will be improved with the combination of SABR and sipuleucel-T, we further hypothesize that the addition of SBRT will increase the durability of response or lengthen the time to progression thus increasing the cost effectiveness of the combined therapies. Thus, we hypothesize that the added treatment of SBRT while adding modestly to the total cost of the combined therapies may be cost saving over the patient's entire treatment course compared to sipuleucel T alone, making the combination a very attractive treatment for mCRPC patients. Additionally, we hypothesize that combination of SBRT and sipuleucel T will increase the quality-adjusted life-years for CRPC cancer patients (compared to the prior reported chemotherapeutic options for mCRPC) at a reasonable incremental cost, as defined by generally accepted cost-effectiveness thresholds. The sample size would be prohibitively large should these secondary endpoints be analyzed beyond simple descriptive statistical purposes.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To evaluate the improvement in the time to progression (TTP) of metastatic prostate cancer after the combined treatment with sipuleucel-T and SABR to

metastatic sites, as compared to the historically reported data with the treatment of sipuleucel-T alone.

2.2 Secondary Objectives

2.2.1 To quantify the amplification in immune response generated by Sipuleucel-T by the addition of SABR.

2.2.2 To evaluate the improvement in the overall survival (OS) of mCRPCa patients after the combined treatment with sipuleucel-T and SABR to metastatic sites, as compared to the historically reported data with the treatment of sipuleucel-T alone.

2.2.3 To evaluate the improvement in the progression free survival (PFS) of mCRPCa patients after the combined treatment with sipuleucel-T and SABR to metastatic sites, as compared to the historically reported data with the treatment of sipuleucel-T alone.

2.2.4 To evaluate the improvement in the biochemical progression free survival (bPFS) of mCRPCa patients after the combined treatment with sipuleucel-T and SABR to metastatic sites, as compared to the historically reported data with the treatment of sipuleucel-T alone.

2.2.6 To evaluate the improvement in the prostate cancer-specific survival (PCaSS) of mCRPCa patients after the combined treatment with sipuleucel-T and SABR to metastatic sites, as compared to the historically reported data with the treatment of sipuleucel-T alone.

2.2.7 To evaluate the adverse events for the first 6 months after completion of radiation therapy associated with Sipuleucel-T when administered in combination with SABR to metastatic sites, as compared to the historically reported data with the treatment of Sipuleucel-T alone.

2.2.8 To evaluate the cost effectiveness and health-related quality adjusted life of the combination treatment of SABR and sipuleucel T in patients with mCRPC.

2.3 Exploratory Objectives

2.3.1 Immunologic Correlates: The objective of the correlative immunologic studies is to characterize the nature of immune response by the measurement of the relative presence of different subpopulations of immunocytes and by the levels of their regulatory cytokines in patient sera as well as within the metastatic sites. In addition, any correlation between the primary and secondary outcomes to cytokine levels or changes in the level of immunocytes will be explored.

2.3.2 Cost-effectiveness and Quality of Life Correlates: An exploratory objective of this study will compare the cost effectiveness and improvement of quality of life of this combination treatment to the other current standards of care for mCRPC patients (i.e. Docetaxel, sipuleucel-T alone, etc.).

2.4 Endpoints

TTP: The primary endpoint of TTP will be measured as described in the recommendations of Prostate Cancer Clinical Trials Working Group 2 [49] and in accordance with the Phase III clinical trial by Kantoff et. al. [10] :

- Progressive disease (PD) on serial radiographic imaging tests
  - Visceral/soft-tissue mets:
    - PD defined using RECIST 1.1 criterion (www.RECIST.com)
    - >50% increase (in the sum of the products of diameters for index lesions) measurable disease
  - Clear worsening of non-measurable disease
  - Bone Lesions: (PCWG2 recommendations; JCO 2008)
    - Appearance of 2 or more new bone lesions in Bone scan, confirmed by a repeat bone scan in ≥6 weeks.
    - The Appearance of 2 new lesions on the first follow-up scan (6 week scan) will require ≥2 additional new lesions in a repeat bone scan ≥6 weeks apart.
- Clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture.

Radiographic imaging including Bone scan and CT scan (PET scan alone or equivocal are acceptable alternatives) will be repeated every 8-12 (+/- 1 week) weeks (since the reported TTP with Sipuleucel-T alone is 14.6 wks) for the first two years after completion of all study treatment and every 6 months thereafter for two years. Bone scans will be repeated every 8-12 (+/- 1 week) weeks for the first 9 months after completion of all study treatment should bone lesions be present pre-study. CT scans will be performed every 8-12 weeks for the first 9 months after completion of study treatment only if soft tissue lesion is present (see section 5 for details).

2.4.1 Immunologic Endpoint: Reaching an immunologic endpoint by any patient will constitute either an amplification of immune response (as compared to historically reported values for sipuleucel-T administration alone) or abscopal radiographic response. Immune response will be measured using ELISpot assay, T-cell proliferation assay or ELISA. The assays will first be calibrated by measuring the background responses in baseline samples of patients pre-treatment and an increase of >95th percentile will be considered a positive response. To reach the immunologic end point for this trial, there has to be a >100% increase in immune response as measured by ANY of the assays when Sipuleucel-T is administered alone as reported by Sheikh et al [32] for patients treated in the IMPACT trial:

- ELISpot Assay (with PA2024 and PAP) showed that the median # of spots were 12, 5 and 8 at Wks 6, 14 and 26 respectively with wk 0

showing 0 spots for PA2024; A 100% increase in the median number of spots from these numbers after normalizing to control (pre-treatment values) at their respective time points will constitute reaching the endpoint.

- T-Cell proliferation (3H-Thymidine) assay showed a median T-Cell Stimulation Index (SI) of 20 at Wk 6 and 18 at Wk 14 and 12 at Wk 26; therefore a 100% increase of SI from these values at their respective time points after normalization to control (pre-treatment values) will constitute reaching the endpoint.
- ELISA showing an increase in >1:400 increase in the titer of antibody to PA2024 is reported by Sheikh et al [32], therefore an increase of 1:800 titer or more would constitute reaching the endpoint.

- A radiographic abscopal effect will be counted as evidence of an immunologic response and will be defined as radiographic response at non-treated sites
  - CT measurement of >50% decrease in diameter of a non-target soft-tissue or visceral lesions (RECIST 1.1) as defined above
  - PR or CR as defined in (Section 6.1.4) and per RECIST 1.1.
  - Resolution of bone lesions in bone scan or a significant improvement in Bone scan as assessed by a radiologist.
  - Since, it may be very difficult to assess a radiographic response in prostate cancer blastic lesions, if there are no progression of disease (as defined above) > 2 standard deviation from the Median TTP (14.6 wks), it will also constitute as evidence of a durable immune response.

2.4.2 PFS: Progression-free survival (PFS) is defined as the length of time from start of treatment (week 0) to the time of disease progression (as defined in Section 6) or death from any cause.

2.4.3 bPFS: Biochemical progression-free survival (bPFS) is defined as the time from start of treatment (week 0) to the time of PSA disease progression with PSA progression defined as the first documented date of an increase in PSA by > 2ng/ml from baseline AND an increase >25% from baseline value that is confirmed by a second measurement >3 weeks apart according to the recommendations of PCWG2 [49], or death from any cause.

2.4.4 OS: OS is defined as the duration of time from start of treatment (week 0) to the time of death from any cause.

2.4.5 Prostate cancer specific survival (PCaSS): PCaSS is defined as the percentage of patients who have not died from prostate cancer at the time of analysis.

2.4.6 Toxicity: Toxicity will be measured and reported based on NCI's CTCAE v4.0 toxicity criteria

2.4.7 Quality of Life: FACT-P, EQ-5D and modified BPI will be used to assess quality of life.

2.4.8 Cost Assessment: Health care utilization data needed to assess costs will be obtained from treatment records to include costs of hospitalization, treatment, ER visits, physician and clinic visits and medications (See section 6.3 and 10 for detail)

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 History of metastatic prostate cancer

3.1.2 Patient must currently be on androgen deprivation or anti-androgen therapy with castrate levels of testosterone (< 50ng/dl)

3.1.2.1 Medical castration should continue until disease progression

3.1.3 Radiographic evidence of metastatic disease documented with bone scan, (CT scan, MRI or any form of PET scan (Axumin, PSMA etc.) are acceptable alternatives)

3.1.3.1 Patients with any number of metastatic sites are allowed to enroll. However, only up to six sites will be selected for SBRT treatment and will be at the discretion of the treating radiation oncologist.

3.1.4 PSA ≥ 0.2 ng/ml that is confirmed with a second PSA measurement

3.1.5 Adequate hematologic, renal, and liver function as evidenced by the following:
White blood cell (WBC) ≥ 2,500 cells/μL
Absolute neutrophil count (ANC) ≥ 1,000 cells/μL

Platelet Count ≥ 100,000 cells/μL
Hemoglobin (HgB) ≥ 9.0 g/dL
Creatinine ≤ 2.0 mg/dL
Total Bilirubin ≤ 2 x upper limit of normal (ULN)
Aspartate aminotransaminase (AST, SGOT) ≤ 2.5 x ULN
Alanine aminotransaminase (ALT, SGPT) ≤ 2.5 x ULN

3.1.6 Previous treatment with surgery, radiation or hormonal therapy is allowed.

3.1.7 Performance status ECOG 0 or 1.

3.1.8 Life expectancy of at least 6 months

3.1.9 Age ≥ 18 years.

3.1.10 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Subject has received chemotherapy within the past 14 days.

3.2.2 Subjects with metastatic disease exclusively present within a previously irradiated field.

3.2.3 Subject is receiving any other investigational agents for the treatment of prostate cancer.

3.2.4 Subjects with known brain metastases..

3.2.5 Subjects with malignant pleural effusions and malignant ascites

3.2.6 Systemic corticosteroid use within past 14 days, unless prescribed in conjunction with Abiraterone. Use of inhaled, intranasal, and topical steroids is acceptable.

3.2.7 Use of any of the following within the past 14 days: Megestrol acetate (Megace®), diethyl stilbestrol (DES), or cyproterone acetate, Ketoconazole, high dose calcitriol [1,25(OH)2VitD] (i.e., > 7.0 μg/week).

3.2.8 Initiation or discontinuation of bisphosponate use within past 14 days.

3.2.9.1 Continuation of use is allowed but patients must continue bisphosphonate throughout the treatment and follow up period until disease progression.

3.2.9 Subjects with spinal cord compression

3.2.10 Paget's disease of bone.

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

3.2.12 History of positive serology tests for human immunodeficiency virus (HIV) 1 and 2, human T cell lymphotropic virus (HTLV)-1, Hepatitis B and C

4.0 TREATMENT PLAN: STUDY MEDICATION

4.1 Sipuleucel-T: Treatment Dosage and Administration – The administration of Sipuleucel-T follows standard-of-care treatment. The following treatment plan is recommended.

4.1.1 Preparation of sipuleucel-T:

Sipuleucel-T will be administered for three cycles, two weeks each as per manufacturer's recommendation. SABR will be administered on the third-fourth week. SABR planning takes place during the first two weeks and sipuleucel-T administration and treatment administration takes place on the third or fourth week, prior to the last leukapheresis. All treatments can be carried out as out-patient. Further information regarding the manufacture and characterization of sipuleucel-T is provided in the sipuleucel-T Prescriber Information (Appendix G).

4.1.2 Leukapheresis and Collection of Quiescent APCs

Collection of blood cells to generate sipuleucel-T is analogous to that for autologous blood transfusions. Briefly, subjects undergo a standard 1.5 to 2.0 blood volume leukapheresis to harvest peripheral blood mononuclear cells (PBMCs; primarily lymphocytes and monocytes), which takes place in the regional Carter Bloodcare center over approximately 4 hours. Prior mobilization with a colony-stimulating factor is not performed. Immediately after collection, the leukapheresis product is transported to a regional manufacturing facility.

4.1.3 Sipuleucel-T

Sipuleucel-T is an autologous cell product consisting of APCs loaded with prostate antigen PA2024. PA2024 is a recombinant fusion protein consisting of human PAP and GM-CSF. GM-CSF acts as a targeting molecule that directs the PAP antigen to APCs and promotes antigen uptake and processing. PAP is a tissue-specific target antigen rather than a tumor-specific target antigen. Studies with specific monoclonal antibodies and RNA probes indicate that the antigen is strictly prostate-specific. Immunohistochemical studies reveal that the antigen is expressed by normal prostate tissue, and > 90% of all prostatic adenocarcinomas, but is not expressed by other tissues [50]. PAP is secreted by the prostate tumor cells in vivo, and an elevated serum level is found in most subjects with advanced prostate cancer [51]. The cDNA for PAP has been isolated. Analysis of sequence homology with other known proteins reveals a low risk of cross-reactivity of immune responses. GM-CSF is a multilineage factor that may also activate mature granulocytes and macrophages, and may activate quiescent APCs.

Preparation of sipuleucel-T entails isolating quiescent APCs from a subject's peripheral blood leukapheresis product by buoyant density techniques and then culturing them for approximately 2 days in the presence of PA2024. The culture medium does not contain serum or exogenous cytokines. During the culture process, APCs specifically and selectively pick up antigen (PA2024) and differentiate into antigen loaded APCs capable of presenting antigen to T cells. These APCs thus represent the cells responsible for the biological activity of sipuleucel-T. Other cell populations in sipuleucel-T co-purify with APCs during buoyant density centrifugation, but do not incorporate or present antigen, and are therefore referred to as "non-APCs." After the culture period, the cells are washed and suspended in Lactated Ringer's Injection, USP. The final preparation of PA2024-loaded APCs is designated sipuleucel-T. Sipuleucel-T is placed in a refrigerated package and transported to the clinical site for infusion.

4.1.4 Quality Testing

Quality control (QC) testing is performed at several time points during the manufacturing process and on samples of the final product. If the final product passes all required release tests, an approval to infuse the product (Cell Product Disposition Form) is faxed to the infusion center. If a cell product does not meet Dendreon quality specifications, Dendreon will contact the infusion center by telephone and by fax. Dendreon will provide instructions for product return or destruction of cell products that are not approved or not infused.

4.1.5 Storage and Time Limitations

The infusion of sipuleucel-T or placebo must begin prior to the expiration time indicated on the product label. Expired cell products must not be infused.

4.1.6 Administration (Recommended)

Subjects are premedicated with acetaminophen and an antihistamine such as diphenhydramine prior to the infusion. After the site receives the Cell Product Disposition Form indicating the cell product is approved, the infusion is administered over approximately 60 minutes through an intravenous (IV) line suitable for blood transfusion (without a cell filter). The infusion of sipuleucel-t contains at least 50 million CD54+ activated DC. Subjects are observed for at least 30 minutes following the infusion.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Leukapheresis			IV over 4 hours **before** Sipuleucel-T	Week 1,3,5	2 weeks (14 days)
Sipuleucel-T	Acetaminophen, diphenhydramine, 30min prior to infusion	>50,000000 CD54+ cells in 250ml LR	IV infusion, 3-4 days after completion of Leukapheresis	week 1, 3, 5	
SABR		21-33Gy/1-3 fractions		Week 3-4	

Sipuleucel-T is an autologous DC therapy, which must be administered only to the patients the cells are derived from. It is essential to confirm identity of the patient and the specimen before infusion. Do not initiate infusion of expired Sipuleucel-T. If Sipuleucel-T is expired, another leukapheresis will have to be scheduled. Infuse Sipuleucel-T intravenously over a period of approximately 60 minutes. Interrupt or slow infusion for acute infusion reactions, depending on the severity of the reaction. The most common adverse reactions (incidence ≥ 15%) are chills, fatigue, fever, back pain, nausea, joint ache, and headache. Sipuleucel-T is not routinely tested for transmissible infectious diseases and may transmit diseases to health care professionals handling the product. Universal precautions should be followed.

4.2 SABR Dose and Techniques

4.2.1 SABR Dose

The SABR dose and fractionation scheme is generated to deliver a potent dose to ablate the targeted lesions and at the same time maximize an immune response. Since multiple studies have shown an influx of lymphocytes and monocytes within 24-48 hours after tumor irradiation [52-55] and these cells play a critical role in antigen presentation and initiation of an adaptive immune response, multiple fraction irradiation which would kill these infiltrating immunocytes, is

discouraged. Therefore a single fraction or three fraction treatment regimen is allowed, and a single fraction treatment is preferred over three fractions. Due to normal organ toxicity and limits of dose constraints, sometimes a three fraction treatment must be undertaken in those cases it is recommended that the treatment course is completed within 7-10 days. Radiation dose-(immune) response studies have shown a linear increase in immune response with increased dose per fraction of radiation without demonstration of a plateau [4, 52, 55, 56]. Two studies have compared 15Gy x 1 with 5Gy x3, and 20Gy x1 with 5Gy x4 and have showed a superior immune response generated by the single fraction radiation [52, 55]. Clinical experience with oligometastatic patients treated at 1-5 sites of disease has also showed an increase in progression free survival with the increasing radiation dose per fraction [57]. A dose of less than 7.5 Gy per fraction has demonstrated lower induction of systemic INF-γ producing cells and therefore 8Gy per fraction is the lowest permitted dose [56].

The SABR prescription dose will be delivered to the periphery of the planning target volume (PTV, see below for definitions). Investigators will have discretion in choosing from either of the biologically equivalent dose levels using one or three fractions, although a single fraction is preferred over three fraction treatments. Treating physician will have further discretion in selecting up to six sites to treat if >6 sites of disease are present. Preference should be given to the largest feasible disease site, bulky progressive sites, symptomatic sites, and sites where palliative and preventative (i.e. to prevent a pathologic fracture in weight bearing bone) indications are applicable. Treating physicians should choose their dose based on established planning guidelines at their center including their ability to respect normal tissue tolerance listed below. It is not required that all targets be treated with the same dose fractionation. A dose from the following table should be used:

Prescription Dose

	Total Cumulative Dose Encompassing 95% of Planning Target Volume (Gy)		
Number of Fractions	Protocol Compliant	Minor Deviation *	Major Deviation
1	21-27 Gy	≥16 Gy, <21 Gy	>27 Gy, <16 Gy
3	26.5-33 Gy	≥24.5 Gy, <26.5 Gy	>33 Gy, <24.5 Gy

*This column is protocol compliant for tumors abutting the spinal cord (major deviation remain as listed)

Dose tolerance limits should be adhered to for all treatments. Protocol compliant dose should be used in all cases, if possible. When treating tumors abutting the spinal cord, tolerance limits should not be exceeded. To facilitate this requirement, minor deviation dose ranges listed above in the table will be considered fully compliant for tumors abutting the spinal cord The gross target/tumor volume (GTV) should be at least $2cm^3$ in size, corresponding to roughly a 1.5 cm diameter tumor. This is to ensure that adequate tumor volume and therefore adequate tumor cells (roughly 10^8 -10^9 cells/cm^3 [58]) are killed for antigen presentation. In addition, it is recognized that for parrallal tissues (i.e. Lung, Liver and Kidney), if tumor lesions are larger than a certain percentage of its total volume, then it becomes exceedingly difficult to reach the tissue constraints and its critical volume dose limit. Therefore, the following GTV volume guidelines should be followed, which is defined for a single lesion:

GTV Volume:

GTV Volume (cc)*		
Protocol Compliant	Minor Deviation *	Major Deviation
2-100	>100; <2; >20% of organ volume	<1.5

*the volume limits only applies to Liver, Lung and Kidney lesions.

4.2.2 Planning Constraints and Concerns

The tolerance dose of SBRT to the gastrointestinal tract is not established, and patients with metastatic disease involving the esophagus, stomach, intestines, or mesenteric lymph nodes will not be eligible. Patients with renal or adrenal metastases are potentially eligible if normal tissue constraints are otherwise met.

It is well established that for palliative effect for a painful bone metastasis, a single dose of 8 Gy is usually as effective as 30 Gy [59]. However, in this protocol the goal is not just to relieve pain within an osseous metastasis but also to dramatically debulk the cancer cells present and induce an immune response, and the higher dose is more likely to accomplish this goal given a higher biological potency [60]. Long term survival after bone metastasectomy has been reported [61]. Irradiation of non-spinal skeletal sites does not generally require specialized techniques of treatment. Metastases in major lower extremity and weight-bearing bones should undergo surgical stabilization if there is radiographic evidence of cortical erosion. Similarly, whenever treating organs of the GI tract (Esophagus, stomach, small/large bowel, rectum), if there are concerns for bowel obstruction, a GI or surgical referral must be placed.

4.2.3 Treatment Technique

Each cycle of Sipuleucel-T consists of two weeks. The first day is a leukapheresis procedure that takes place in the Carter BloodCare: 4201 Gaston Avenue, Dallas, TX 75246; (214) 217-5676. On day 3-4, Sipuleucel-T, which is commercially available from Dendreon, is infused to the patients. This cycle is repeated every two weeks for a total of three times. SABR planning simulation takes place during the first cycle of Sipuleucel-T and the SABR treatment is administered over the two weeks of cycle 2.

4.2.3.1 Simulation, beam arrangements, tumor prescription dose

Treatment to skeletal lesions other than spine, may be accomplished with any 3D conformal radiotherapy or intensity-modulated radiotherapy (IMRT) technique suitable for this application with performance specifications adequate to provide proper tumor dose distribution and normal tissue sparing. The bone lesions can be treated with a conformal 3D or IMRT technique, which is different than SBRT/SABR technique. The difference lies in immobilization technique and dosimetric planning, but otherwise all the descriptions of SBRT in terms of contouring and tissue constraints that needs to be met remains the same. Immobilization for 3D or IMRT does not require a body frame but rather a Vac-lock bag is used with appropriate additional devices (i.e. head rest, knee sponge, etc.).

At the time of simulation for patients who will receive SBRT to the lung and/or liver, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during treatment if no breathing control device is used. Patients will be assessed for suitability for tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required.

With the patient immobilized in a vacuum-type or equivalent body mold preferably in a body frame, a planning CT scan with 3-5 mm slices is performed. Intravenous contrast is recommended for lesions near mediastinal structures and lesions within the liver. The form of respiratory control to be used during treatment should also be used during the simulation. Oral GI contrast to highlight the stomach and duodenum is recommended for patients with medial liver lesions or lesions of the caudate lobe.

For treatment to the liver, the following structures are contoured: entire liver, each individual liver gross tumor volume (GTV), each kidney, and the spinal cord. The planning target volume (PTV)

is constructed to account for the positional uncertainty of the GTV during treatment. The PTV for each contoured GTV should be at least 5mm larger than the GTV in the axial plane and 1.0 cm larger than the GTV in the craniocaudal plane. Larger margins may be used in cases where greater motion of the hemidiaphragm is observed in simulation despite standard maneuvers to diminish motion. For lung SBRT the same principles apply; the entire lung volumes are contoured, as are each individual GTV within the lung.

The prescription dose for each lesion is listed in the table in section 4.1, prescribed to the periphery of the PTV. In case of IMRT or 3D conformal technique, a PTV coverage of >95% of the prescription dose is required with no restrictions on dose heterogeneity other than minimal PTV dose >90%. There is no restriction on the dose "hotspot" except that it must be located within the PTV. A Linear Accelerator with effective photon energies of ≥ 6 MV is required. The use of a Multi-leaf collimator (MLC) or custom blocks are acceptable. A stereotactic relocalization system that relies upon stereoscopic radiographs, implanted fiducials, or near real-time CT based verification will be used.

The PTV may be treated with any combination of coplanar or non-coplanar three-dimensional conformal fields, shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by the planning system to produce the optimal conformal plan in accordance with volume definitions.

4.2.3.2 Normal Tissue Dose Constraints

In accordance with the prior Phase I studies [62], certain normal tissue dose constraints must be respected.

The possibility that SBRT-induced fibrosis might cause occlusion of large central airways, thus impeding ventilation distal to the occlusion has been well considered [63]. An adjustment to the fractionation scheme may be made if, in the opinion of the treating radiation oncologist, the following conditions apply: (1) the location of a lung lesion is close enough to a large proximal bronchial airway such that occlusion might occur, and (2) compromised ventilation to the segment(s) of lung potentially affected would cause clinically significant adverse consequences. In such a case, the treating radiation oncologist should discuss any proposed dose modifications with the PI to decide whether a regimen of similar biological potency can be safely given.

The same special situations apply whenever a lesion is close to the spinal cord, small bowel, great vessels, porta hepatis and renal pelvis. In these situations, in addition to meeting dose constraints, additional tests must be performed to ensure adequate reserve of normal tissue function. For example, in the situation of a renal pelvis lesions, a functional renal scan must be performed to ensure ample renal reserve for the patient. In case of a patient with COPD receiving radiation to lung lesions, PFT must be performed to demonstrate FEV1>1.2L and DLCO >60%. In case of a patient with peripherial lung lesion close to the ribs, to decrease the chance of a rib fracture, the lesion must be >3mm from the rib. In case of treating liver lesions, LFTs must be within normal range.

Special condition applies in the setting of a patient whose primary prostate disease has been irradiated previously and is present as a site of disease. Since re-irradiation toxicity is a concern, these patients will not receive SABR to the sites of previous irradiation. These patients will only be included in the trial if they have metastatic disease that are eligible for SABR outside the previously irradiated field. Re-irradiation to a site that has received previous SBRT is also not allowed.

Deviations from the intended dose regimen will be documented, with calculations of the BED of the applied regimen included in the patient's research chart along with documentation of the discussions pertaining to the idiosyncrasies of the case.

Prescription Volume (ml)

	Total Cumulative Dose Encompassing 95% of Planning Target Volume (Gy)		
Number of Fractions	Protocol Compliant	Minor Deviation *	Major Deviation
1	21-27 Gy	≥16 Gy, <21 Gy	>27 Gy, <16 Gy
3	26.5-33 Gy	≥24.5 Gy, <26.5 Gy	>33 Gy, <24.5 Gy

*This column is protocol compliant for tumors abutting the spinal cord (major deviation remain as listed)

The following table lists the specific organ and dose fractionation constraints on normal tissues.

For One Fraction:

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	8 Gy	10 Gy	neuritis
Cochlea			9 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc <1.2 cc	10 Gy 8 Gy	14 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	10 Gy	14 Gy	myelitis
Cauda Equina	<5 cc	14 Gy	16 Gy	neuritis
Sacral Plexus	<5 cc	14.4 Gy	16 Gy	neuropathy
Esophagus*	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	13.6 Gy	16.4 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	17.4 Gy	20.2 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	12.4 Gy	13.3 Gy	stenosis with atelectasis
Rib	<5 cc	28 Gy	33 Gy	Pain or fracture
Skin	<10 cc	25.5 Gy	27.5 Gy	ulceration
Stomach	<5 cc	17.4 Gy	22 Gy	ulceration/fistula
Bile duct			30 Gy	stenosis
Duodenum*	<5 cc <10 cc	11.2 Gy 9 Gy	17 Gy	ulceration
Jejunum/Ileum*	<30 cc	12.5 Gy	22 Gy	enteritis/obstruction
Colon*	<20 cc	18 Gy	29.2 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	39 Gy 22 Gy	44.2 Gy	proctitis/fistula
Ureter			35 Gy	stenosis
Bladder wall	<15 cc	12 Gy	25 Gy	cystitis/fistula

Penile bulb	<3 cc	16 Gy		impotence
Femoral Heads	<10 cc	15 Gy		necrosis
Renal hilum/vascular trunk	15 cc	14 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.6 Gy	V-8Gy <37%	Pneumonitis
Liver	700 cc	11 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	9.5 Gy		Basic renal function

For Three Fractions:

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)****	**Endpoint (≥Grade 3)**
Optic Pathway	<0.2 cc	15.3 Gy	17.4 Gy	neuritis
Cochlea			14.4 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	15.9 Gy	23.1 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc <1.2 cc	15.9 Gy 13 Gy	22.5 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	18 Gy	22.5 Gy	myelitis
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	neuritis
Sacral Plexus	<5 cc	22.5 Gy	24 Gy	neuropathy
Esophagus*	<5 cc	17.7 Gy	25.2 Gy	stenosis/fistula
Brachial Plexus	<3 cc	22 Gy	26 Gy	neuropathy
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis
Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	25.8 Gy	30 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	18.9 Gy	23.1 Gy	stenosis with atelectasis
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc <10 cc	15.6 Gy 12.9 Gy	22.2 Gy	ulceration
Jejunum/Ileum*	<30 cc	17.4 Gy	27 Gy	enteritis/obstruction

Colon*	<20 cc	24 Gy	34.5 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	45 Gy 27.5 Gy	49.5 Gy	proctitis/fistula
Ureter			40 Gy	stenosis
Bladder wall	<15 cc	17 Gy	33 Gy	cystitis/fistula
Penile bulb	<3 cc	25 Gy		impotence
Femoral Heads	<10 cc	24 Gy		necrosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	10.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	11.4 Gy	V-11Gy<37%	Pneumonitis
Liver	700 cc	17.1 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15 Gy		Basic renal function

*Avoid circumferential irradiation.
** "point" defined as 0.035cc or less
Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation.
Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

4.2.4 Radiation Therapy Quality Assurance

Dr. Timmerman will perform an RT Quality Assurance Review after complete data for the first 15 cases enrolled has been received at the University of Texas Southwestern.

4.3 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity for 6 months following the completion of radiation therapy(see Time and Events table (5.4)). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Both treatments of sipuleucel-T and SABR have excellent safety profile. The most commonly reported toxicity for sipuleucel-T (incidence ≥ 15%) are chills, fatigue, fever, back pain, nausea, joint ache, and headache (see Section 7.0 and 8.0 for detail). Acute infusion reactions (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the sipuleucel-T group developed an acute infusion reaction. The most common events (≥ 20%) were chills, fever, and fatigue. In 95.1% of patients reporting acute infusion reactions, the events were mild or moderate. Fevers and chills generally resolved within 2 days (71.9% and 89.0%, respectively). In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the sipuleucel-T group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs. 0.8% following

the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the sipuleucel-T group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the sipuleucel-T group.

In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.

Hematologic toxicity is not reported or expected for either sipuleucel-T or SABR.
Non-hematological Toxicities should be managed as follows:

Non-hematological Toxicity Dose Reductions		
NCI CTC Grade	**Sipuleucel-T**	**SABR**
0-2	No change from original starting dose	No change from original starting dose
3	Hold until resolved to ≤Grade 2, then proceed	Hold until resolved to ≤Grade 2, then proceed
Second episode of grade 3 or 4 toxicity	Hold until resolved to ≤Grade 2, then proceed	Hold until resolved to ≤Grade 2, then proceed
Third episode of grade 3 or 4 toxicity	Remove subject from trial	Remove subject from trial

4.4 Concomitant Medications/Treatments

Drugs that are prohibited during or within the follow up time of the protocol therapy include chemotherapy, glucocorticoids and any other treatments directed to mCRPC patients. Bisphosphonates or treatment for bony metastatic disease and androgen deprivation therapy should not be initiated, but if patient is already on the treatment, then it should be continued throughout the duration of the study.

4.5 Duration of Therapy

Treatment administration is typically completed within 6 weeks from the start of first Sipuleucel-T. In case of delay, the recommended time for completion of both Sipuleucel-T and SABR is within 8 weeks. In the absence of treatment delays due to adverse events, treatment may continue until:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

Subjects will be followed for four years or death, whichever occurs first. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. The follow-up will be every 8-12 weeks for the first 6-36 weeks or until 9 months with physical exam., then every 12 weeks until two years, then every 6 months for two years. PSA for bRFS will be measured every three months for 2 years and every 6 months thereafter for the following 2 years. See section 5.0 for detail. Once the subject demonstrates progressive disease (documented by two sets of imaging at least 8 weeks apart), they will no longer adhere to the study calendar and will be followed for survival only.

4.7 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per standard of care.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. If the (specially radiographic) studies were done before informed consent was obtained for clinical indications (not exclusively to determine study eligibility), they may be used for baseline values ONLY if they were done within 30 days prior, to keep within the limits of starting Sipuleucel-T within 30 days(+/-7days) of baseline radiologic study.

All screening procedures must be performed within 30 days (+/-7) prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry according to Appendix A.

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed. See section 7 for Adverse Event monitoring and reporting.

5.1.9 *Hematology*

CBC with differential.

5.1.10 *Blood draw for correlative studies*

Only if patient has met the eligibility and has signed informed consent. See Section 9.0 for details.

5.1.11 *Serum chemistries*

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose and total bilirubin.

Additional required lab work:

Uric acid, C-Reactive protein (CRP), beta-2 microglobulin, LDH

Prostate cancer specific tests: PSA, testosterone

5.1.12 Serologic Tests

HLA typing (Human Leukocyte Antigen). This test is genetic so may be performed at any time prior to registration.

5.1.13 *Radiographic Imaging*

Bone scan, CT chest, abdomen and pelvis with IV contrast. PET scan alone can replace both the bone and CT scans.

5.1.15 *QoL Questionnaires*

FACT-P, EQ-5D, modified BPI, cost and convenience questionnaire. These forms will be referred to collectively as QoL Questionnaires.

5.2 Procedures during treatment (performed per MD discretion)

Each cycle of Sipuleucel-T consists of two weeks. The first day is a leukapheresis procedure that takes place in the Carter BloodCare: 4201 Gaston Avenue, Dallas, TX 75246; (214) 217-5676. On day 3-4, Sipuleucel-T, which is commercially available from Dendreon, is infused to the patients. This cycle is repeated every two weeks for a total of three times. SABR planning simulation takes place during the first cycle of Sipuleucel-T and the SABR treatment is administered over the two weeks of cycle 2.

5.3 Follow-up Procedures

Subject will be followed every 8-12 weeks after completion of (or early withdrawal from) study treatment (Sipuleucel-T) until nine months. After nine months, subjects will be followed for every 12 weeks for a total of 2 years; every six months for another two years. After four years, the subject follow up will be at the discretion of the treating physician. Once the subject demonstrates progressive disease (documented by two sets of imaging at least 6 weeks apart) they will no longer adhere to the study calendar and will be followed for survival only.

5.4 *Time and Events Table*

	Pre-study	Cycle 1, Day1	Cycle 2, Day15 – 28 (+/- 5 days)	Cycle3, Day29 – 32 (+/- 5 days)	Week 6-36 (9 months): Q8-12 weeks	Months 9-24: q12 weeks	Months 24-48: q6 months
Informed Consent	X						
Vital Signs	X	X	X	X	X	X	X
History and PE	X				X[2]	X	X
Performance Status	X				X	X	X
Adverse event monitoring	X				X[A]		
Bone Scan[9]	X				X[1]	X	X

CT Chest, Abd, pelvis w/ Contrast[9]	X				X[3]	X	X
CBC	X				X	X	X
Comprehensive Chemistry	X				X	X	X
Uric acid, Beta-2 microglobulin, C reactive protein, LD	X				X (at 6 weeks and 12 weeks only)		
HLA typing[6]	X						
PSA, Testosterone	X				X	X	X
Blood collection for Immune Assays	X		X		X[4]		
SABR			X				
QOL Questionnaires (baseline, 6 months and 1 year only)	X				X[5]	X	
Cost and Convenience Questionnaire					X (at first f/u only)		

[1] Bone scan performed every 8-12 weeks only if bone lesions present at baseline. All other patients receive bone scan every 12 weeks.
[2] Physical Exam only.
[3] CT scans performed every 8-12 weeks only if soft tissue lesion is present. All other patients receive CT scans every 12 weeks.
[4] Immunologic blood collection is pre-study, after SABR tx, and 6 weeks, 12 weeks, and 24 weeks after completion of cycle 3 Sipuleucel-T.
[5] Cost and Convenience Questionnaire will only be administered at the first follow up visit. QoL surveys will take place pre study, 24 weeks and one year after completion of cycle 3 Sipuleucel-T
[6] HLA typing (baseline only)

[7]Post tx biopsy of metastatic site – (elective post-tx bx at 8 weeks see Section 5.3)

[9] PET scan alone is an acceptable alternative to both CT CAP and bone scan.
[A] Adverse events will only be collected and documented from baseline to the first 6 months following completion of radiation therapy

Note that the study calendar is based on the ideal subject. The schedule should be followed as closely and realistically as possible, but may be modified due to problems such as scheduling delays, weekends, conflicts such as clinic closure or poor weather conditions, or other unforeseeable events.

5.5 Removal of Subjects from Study

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

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements; including if patient fails to receive at least two cycles of Sipuleucel-T.

5.5.4 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.5 Treating physician judges continuation on the study would not be in the subject's best interest;

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

5.5.7 Lost to follow-up. If a research subject cannot be located to document survival after a period of six months, the subject may be considered "lost to follow-up." All attempts to contact the subject during the six months must be documented.

6.0 Measurement of Effect

6.1 Antitumor Effect

Response and progression will be evaluated in this study using the modified new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee [*JNCI* 92(3):205-216, 2000] with modifications suggested by PCWG2 [49] recommendations and as used in the Phase III clinical trial by Kantoff et. al.[10]. Changes in only the largest diameter (one-dimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria as outlined in http://www.recist.com/.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with Sipuleucel-T.

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

6.1.2 Disease Parameters

6.1.2.1 Bone Lesions: PCWG2 recommendations will be followed for bone lesions as follows:

Bone Lesions: (PCWG2 recommendations; JCO 2008)

- Radiotracer uptake in a radionuclide bone scan consistent with metastatic disease as read by a radiologist.

6.1.2.2 **Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:**

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

3. 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease.

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions.

All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions

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

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up using appropriate radiologic imaging.

Bone scans and CT scan of Chest, abdomen and pelvis with IV contrast will be performed at baseline. If patient has bone lesions, then bone scan will be performed every 8-12 week intervals for 36 weeks and CT scan performed every 12 weeks. If patient has soft-tissue lesions, then CT scan will be performed every 8-12 weeks and bone scan performed every 12 weeks until 36 weeks (Please see section 5.3 and 5.4 for detail).

Spiral CT and MRI. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

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

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions.

6.1.4.2 Evaluation of Non-Target Lesions

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

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

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

6.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference

for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

A 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

6.1.5 Duration of Response

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

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

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

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.1.6.1 Evaluation of Bone Lesions:

6.1.6.1.1 Progression of bone lesions will be defined according to the PCWG2 criterion:

- Appearance of 2 or more new bone lesions in Bone scan, confirmed by a repeat bone scan in ≥8 weeks.
- The Appearance of 2 new lesions on the 6 week scan will require ≥2 additional new lesions in a repeat bone scan ≥8 weeks apart.

6.1.6.1.2 Response of bone lesions will be defined by either a complete resolution (CR) at the metastatic sites or partial resolution (PR) of radiotracer uptake by a radiologist.

6.1.6.2 Evaluation of Pathologic Fracture:

Any clinical suspicion of pathologic fracture will prompt radiologic evaluation with plain film, CT or MRI as appropriate and if confirmed by a radiologist, will constitute progression.

6.1.6.3 Evaluation of spinal cord Compression or Cauda equina compression:

Any clinical suspicion of cord or cauda equine compression will prompt radiologic evaluation with MRI (CT myelography if patient is not eligible for MRI) as appropriate and if confirmed by a radiologist, will constitute progression.

6.1.7 Time to Progression (TTP)

TTP is measured from the time treatment is started (week 0) until the first date that progressive disease is objectively documented as defined by one of the response criterions in 6.1.4.

6.1.8 Measurement of Immunologic Response:

Reaching an immunologic endpoint by any patient will constitute either an amplification of immune response (as compared to historically reported values for sipuleucel-T administration alone) or abscopal radiographic response. Immune response will be measured using ELISpot assay, T-cell proliferation assay or ELISA. The assays will first be calibrated by measuring the background responses in baseline samples of patients pre-treatment and an increase of >95th percentile will be considered a positive response. To reach the immunologic end point for this trial, there has to be a >100% increase in immune response as measured by ANY of the assays when Sipuleucel-T is administered alone as reported by Sheikh et. a.[32] for patients treated in the IMPACT trial:

- ELISpot Assay (with PA2024 and PAP) showed that the median # of spots were 12, 5 and 8 at Wks 6, 14 and 26 respectively with wk 0 showing 0 spots for PA2024; A 100% increase in the median number of spots from these numbers after normalizing to control (pre-treatment values) at their respective time points will constitute reaching the endpoint.
- T-Cell proliferation (3H-Thymidine) assay showed a median T-Cell Stimulation Index (SI) of 20 at Wk 6 and 18 at Wk 14 and 12 at Wk

26; therefore a 100% increase of SI from these values at their respective time points after normalization to control (pre-treatment values) will constitute reaching the endpoint.
- ELISA showing an increase in >1:400 increase in the titer of antibody to PA2024 is reported by Sheikh et.al [32], therefore an increase of 1:800 titer or more would constitute reaching the endpoint.

- A radiographic abscopal effect will be counted as evidence of an immunologic response and will be defined as radiographic response at non-treated sites
  - CT measurement of >50% decrease in diameter of a non-target soft-tissue or visceral lesions (RECIST 1.1) as defined above
  - PR or CR as defined in (Section 6.1.4) and per RECIST 1.1.
  - Resolution of bone lesions in bone scan or a significant improvement in Bone scan as assessed by a radiologist.
  - Since, it may be very difficult to assess a radiographic response in prostate cancer blastic lesions, if there are no progression of disease (as defined above) > 2 standard deviation from the Median TTP (14.6 wks), it will also constitute as evidence of a durable immune response.

6.1.9 PFS:

Progression-free survival (PFS) is defined as the length of time from start of treatment (week 0) to the time of disease progression (as defined in Section 6) or death from any cause.

6.1.10 bPFS:

Biochemical progression-free survival (bPFS) is defined as the time from start of treatment (week 0) to the time of PSA disease progression with PSA progression defined as the first documented date of an increase in PSA by > 2ng/ml from baseline AND an increase >25% from baseline value that is confirmed by a second measurement >3 weeks apart according to the recommendations of PCWG2 [49], or death from any cause.

6.1.11 OS:

OS is defined as the duration of time from start of treatment (week 0) to the time of death.

6.1.12 Prostate cancer specific survival (PCaSS):

PCaSS is defined as the percentage of patients who have not died from prostate cancer at the time of analysis and will be calculated according to the following equation:

$$PCaSS = \frac{Total\ Patients - death\ due\ to\ prostate\ cancer}{Total\ Patients} X\ 100$$

6.2 Quality of Life:

6.2.1 Functional Assessment of Cancer Therapy-P (FACT-P)

Patient-reported functional status will be assessed with prostate cancer subscales of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) (See appendix for form). The FACT-P is a 39-item questionnaire that uses 5-point Likert-type response choices (0 = not at all; 1 = a little bit; 2 =somewhat; 3 = quite a bit; 4 = very much). It will take less than 10 minutes to complete the questionnaire. The Trial Outcome Indices (TOI) also will be utilized to measure the summed functional well-being, physical well-being, and the additional concerns (prostate) subscales of the FACT-P [64, 65]. A 5-point deterioration in the FACT-P TOI between pre-treatment and at year 1 will be considered clinically significant [66].

The first analysis of change in QOL from baseline to 6 weeks will only be performed on patients who are still alive at 6 weeks. Changes in QOL will be also analyzed using all available data at pre study, 6 months and one year with semiparametric generalized estimating equations (GEE).

Additionally, similarly we will also compare the percentage of patients with an effect size for the change in FAPSI (FACT Advanced Prostate Symptom Index) scores between pre-treatment and 1 months which will allow us to compare the percentage of patients whose functional status remains more similar to baseline levels.

6.2.2 EQ-5D

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete (See appendix for form). The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added.

The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score or the cost-utility equation can be used in the quality adjusted survival analysis depending on the health state(s) of interest.

6.3 Cost effectiveness data collection:

Health care utilization data needed to assess costs will be obtained from treatment records. Additionally, in order to assess the treatment related indirect costs and patient out of pocket costs, at the first follow up visit 6 weeks after the completion of cycle 3 Sipuleucel-T(see Appendix VII).

Hospitalizations:. For hospitalizations with physician billing records, impatient physician costs will be estimated by applying Medicare payment rates under the RBRVS-based Medicare Fee Schedule to billed procedures in the physician billing records.
Treatment Cost: Direct costs of radiation treatment including consultation, simulation, treatment planning, and treatment delivery. Patient bills related to treatment will be obtained and estimated by total billed charges adjusted by facility-specific cost-to-charge ration from Medicare cost reports as described above.
Emergency Room visits: The date of ER visit and name of the facility, and whether the ER visit resulted in a hospital admission. ER costs will be estimated using Medicare average payment rates for facility and physician charges, using the merged MEDPAR and MBS data as described above.

Physician and Clinic Visits: The date of the visit, the name of the physician or physician clinic, and the service provided (physician exam, lab test, physical therapy, etc.). Costs for physician and clinic visits will be calculated based on billing records obtained for such visits, using Medicare payment rates for procedures indicated in the clinic billing records. Medications: Prescription drugs used, including dosage strength and frequency of administration. Information about name, dose, and frequency of all prescription medications will be recorded. The medications used by the study patients will be assigned an NDC drug code. Unit costs for these drugs will be estimated as the "AWP" price published in the Red Book less 15%. Outpatient drug costs will be calculated by multiplying unit cost by the number of pills used per day times the length of time the patient received the medication. Note that costs of drugs administered through a clinic (e.g., reimbursed under Medicare Part B) are included under "clinic visit costs" and impatient drug costs are included under "inpatient facility costs." For example: Cost estimated for the Sipuleucel-T infusions will be based on Medicare allowable utilizing J code J3490 and associated facility charges for administration of Sipuleucel-T.

6.4 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

7.0 ADVERSE EVENTS

* To be collected from baseline to six months post-radiation therapy.

7.1 Sipuleucel-T

For the most recent safety update, please refer to the manufacturer's website: http://www.provenge.com/

7.1.1 Contraindications: None

7.1.2 Special Warnings and Precautions for Use:

Sipuleucel-T is intended solely for autologous use

7.1.3 Interaction with other medications:

No studies of drug interactions have been performed with Sipuleucel-T

7.1.4 Adverse Reactions

The most common adverse reactions (incidence ≥ 15%) are chills, fatigue, fever, back pain, nausea, joint ache, and headache. To report suspected adverse reactions, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Incidence of Adverse Events Occurring in ≥ 5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	591 (98.3)	186 (30.9)	291 (96.0)	97 (32.0)
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	591 (98.3)	186 (30.9)	291 (96.0)	97 (32.0)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

* Control was non-activated autologous peripheral blood mononuclear cells.

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing a probably or definitely related to adverse event will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they

can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through *90* days post treatment will be considered acute adverse events.

Late Adverse Events (**as applicable**)

7.2.2 Adverse events occurring in the time period from the end of acute monitoring, to 2 years post treatment, will be defined as late adverse events.Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the subject was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.2.3.1 Results in death.

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

7.2.3.2 Is immediately life-threatening.

(The subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.2.3.3 Requires in-patient hospitalization for greater than 24 hours

7.2.3.4 Results in persistent or significant disability or incapacity.

7.2.3.5 Is a congenital anomaly/birth defect

7.2.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the subject, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.2.4 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research

protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.3 Reporting Requirements for Serious Adverse Events

All SAEs must be reported to Dendreon within 24 hours of being made aware of the SAE. Notification can be made via phone or telefacsimile using an SAE Report Form to be provided by Dendreon. Sponsor investigator shall notify institution, co-investigators and IRB immediately during the conduct of the study and/or after the study is completed should it become aware of information related to the study that would impact participant safety or clinical care. Institution shall promptly disclose such information to study participants.

Dendreon Corporation	
Attn:	Safety Manager
Facsimile:	(206) 829-1647
Phone:	(206) 219-7899
After Hours:	(206) 274-6774

Significant new information regarding an ongoing SAE and the resolution must be sent to Dendreon within 3 business days of awareness of the new information to Dendreon on the SAE Report Form.

For serious adverse event reporting please see table below.

Local Adverse Event - Serious (Occurring to a subject enrolled on a protocol under the UT Southwestern IRB jurisdiction) • All local Serious Adverse Events are reportable to the IRB based on current guidelines.	Within 2 working days of PI Awareness *Reporting of Serious Adverse Events unrelated to study participation is required for interventional studies only.

All clinical trials are reviewed on a monthly basis for enrollment. All local SAEs are reviewed by Radiation Oncology DSMC monthly for severity and attribution. For investigator-initiated trials, all SAEs at affiliated institutions are monitored as local SAEs. The principle investigator and study coordinator will present a study treatment summary and SAEs for review. Source documents will be available for the DSMC members during the review. NCI Common Toxicity Criteria Version 4 will be used for grading and attributing adverse events.

7.3.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Dr. Raquibul Hannan (Ph. No: 214-645-8525
Written reports to: Sarmsitha Sen, Clinical Research Manager Phone: 214-645-1477 UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

7.4 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy Attribution categories are as follows:

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

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.5 Reporting Requirements for Adverse Events

7.5.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, that is study drug related, occurring during the study or within 30 days of the last administration of the study drug.
- Suspected adverse reactions will also be reported to Dendreon Corporation at 1-877-336-3736 and FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
- The IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

7.5.2 Routine Reporting

- All other adverse events- such as those that are expected, or are unrelated to the study participation- are to be reported annually as part of regular data submission.

7.6 Stopping Rules

The study will be stopped if the combination treatment of SABR and Sipuleucel-T in the interim annual analysis is determined to confer significantly increased Grade 3-5 toxicity as reported in the literature from the treatments performed alone.

8.0 DRUG INFORMATION

8.1 Sipuleucel-T

- Other names for the drug(s): Provenge
- Classification - type of agent: autologous cellular immunotherapy
- Mode of action: Sipuleucel-T is an autologous cellular immunotherapy. While the precise mechanism of action is unknown, Sipuleucel-T is designed to induce an immune response targeted against PAP, an antigen expressed in most prostate cancers. During ex vivo culture with PAP-GM-CSF, APCs take up and process the recombinant target antigen into small peptides that are then displayed on the APC surface.
- Storage and stability: Sipuleucel-T arrives in a cardboard shipping box with a special insulated polyurethane container inside. The insulated container and gel packs within the container are designed to maintain the appropriate transportation and storage temperature of Sipuleucel-T until infusion. Once the Sipuleucel-T infusion bag is removed from the insulated container, it should remain at room temperature for no more than 3 hours.
- Protocol dose: Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF
- Preparation: Upon receipt, the outer cardboard shipping box should be opened to verify the product and patient-specific labels located on the top of the insulated container. Infusion must begin prior to the expiration date and time indicated on the cell product disposition form and Product Label. Once the patient is prepared for infusion and the cell product disposition form has been received, remove the sipuleucel-T infusion bag from the insulated container and inspect the bag for signs of leakage. Contents of the bag will be slightly cloudy, with a cream-to-pink color. Gently mix and re-suspend the contents of the bag, inspecting for clumps and clots. Small clumps of cellular material should disperse with gentle manual mixing. Do not administer if the bag leaks or if clumps remain in the bag. Prior to Sipuleucel-T infusion, match the patient's identity with the patient identifiers on the cell product disposition form and the Sipuleucel-T infusion bag.
- Route of administration for this study: IV infusion
- Incompatibilities: There are no known incompatibilities of sipuleucel-T.
- Availability: Commercially available from Dendreon Corporation.
- Side effects: The most commonly reported toxicity for sipuleucel-T (incidence ≥ 15%) are chills, fatigue, fever, back pain, nausea, joint ache, and headache. Acute infusion reactions (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. Please refer the package insert for a detailed list of adverse reactions.

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to measure the induced immune response to not only PAP but to other prostate cancer antigens as well (see section 1.5 for detail). In addition, the correlative studies will evaluate the immune response generated by Sipuleucel-T and the augmentation of the anti-tumor immune response. The submission of collected whole blood before, during and post treatment at 8wk intervals is mandatory. Patient specimen may be shipped to companies or outside institutions to perform specialized assays, a non-extensive list of which is provided below. Specimens will be shipped de-identified.

9.1 Sample Collection Guidelines

Samples will be labeled with the subject's de-identified study number and collection date and delivered for analysis during regular business hours to: NC7: 208; Attn Dr. Raquibul Hannan. These samples will be kept indefinitely, unless the participant withdraws participation in this clinical trial in which case they will then be *destroyed*.

9.1.1 Whole blood sample: Patient's whole blood will be collected in EDTA (Lavender top) tubes for ~ 100 ml at baseline (pre-study), after SABR, at 6 weeks post treatment (post treatment defined as being after administration of cycle 3 Sipuleucel-T), at 12 weeks and at 24 weeks post treatment. In addition, 10 ml will be collected in anti-coagulant-free tubes for the collection of sera. The blood will be processed by centrifugation (1000g, 15min, 4^{o}C), collecting the supernatant and freezing at -80^{o}C in 5 aliquots for future experiments. The pellet will be re-suspended in PBS and PBMC will be isolated using standard protocol. Briefly, the cell suspension will be carefully placed on 10ml polystyrene tube containing 1ml ficoll and centrifuged (400g, 30min, RT). Collect the PBMC region from the ficoll and washed 3x with PBS. Count and freeze cells in 5 aliquots with 10%DMSO 90%FBS in -80^{o}C.

9.2 Assay Methodology

9.2.1 Elispot: IFN-γ ELISpot assays will be performed according to manufacturer's protocol using a commercial ELISpot kit (MabTECH). Briefly, 96 well plates are coated overnight with 0.015 mg/ml of an anti-human IFN-g monoclonal antibody. PBMC from patients will be incubated in triplicates wells and stimulated in the presence of either PA2024 (10µg/ml), protein lysate from patient biopsy (50µg/ml) or 5 ng/ml PMA and 0.5 ng/ml ionomycin as positive control and albumin as negative control. For ELISPOT assays, plates are incubated for 48 hours, washed, probed with biotinylated anti-IFNg, further washed, and then incubated with streptavidin alkaline phosphatase. Spot development is achieved with 5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium (BCIP/NBT; Invitrogen) and spots are enumerated by an automatic ELISpot reader.

9.2.2 ELISA: In this procedure, purified antigen (PAP imunodominant epitope, PA2024, PSA or etc.) is first adsorbed to an EIA 96 well microplate (Fischer). Patient plasma is then added to each well as a source of primary antibody and serially diluted. After extensive washes, detection enzyme (HRP)-linked anti-human mAb is then added to each well and allowed to bind. Appropriate substrate is then added to each well and color development occurs within 5-60 min. UV Microplate Reader will be used to read the plates

9.2.3 ^{3}H-thymidine Proliferation Assay: PBMC from patients will be incubated in a similar manner as above for five days at 37 ^{o}C then overnight with 0.5 mCi tritiated

^{3}H-thymidine, harvested onto a glass-fiber filter using a 96-well FilterMate cell harvester. The radioactivity of the ^{3}H-thymidine is detected by a direct betaplate counter. The degree of antigen-specific clonal T cell expansion will be expressed as a stimulation index (SI) of the ratio of ^{3}H-thymidine incorporation by cells incubated with PA2024 compared with media controls. An alternate method utilizing FACS analysis with carboxy fluorescein diacetate succinimidyl ester (CFSE) is also available [69].

9.2.4 **Chromium Release Cytotoxicity Assays**: For cell-mediated cytotoxicity analysis, A 50 µl sample of ^{51}Cr-labeled target cells (LNCaP or PC3 human prostate cancer cell) is mixed with 100µl of effector cells (patient PBMC) at various target to effector ratio (E:T ratios). After centrifugation at 100 X G, the cells are incubated for 2 hr at 37°C. The radioactivity of culture supernatant is measured using a gamma counter and percentage of cytotoxicity is calculated. For antibody-dependent cytotoxicity analysis this procedure will be performed with patient's plasma instead of PBMC and the percentage of cytotoxicity is calculated in similar manner. An alternate and non-radioactive labeling method utilizes GAPDH enzyme release from lysed cells called Bioluminescence Non Radioactive Cytotoxicity Assay (aCella-TOX, T Cell Technology, INC) [70, 71].

9.2.5 **Flow cytometric analysis (FACS):** For FACS analysis of cell-surface molecules, the cell samples are stained with fluorescent dye – conjugated monoclonal antibodies against the selected markers on ice followed by fixation with 4% paraformaldahyde. Data are acquired on a LSRII (BD Biosciences) and analyzed using FACSDiva software (BD Biosciences). The PBMC of each patient before and after treatment will be analyzed to identify the relative sub-population of CTLs, regulatory T-Cells, effector memory T cells, MDSCs, neutrophils and NK cells utilizing appropriate cell surface markers (see section 1.5).

9.2.6 **Immunohistochemical staining (IHC):** Standard immunohistochemistry staining procedure will be performed using the Benchmark XT automated stainer (Ventana) for both antibodies. Briefly, formalin-fixed, paraffin-embedded tissue sections will be cut at 3-4 micron and air-dried overnight. The sections will be deparaffinized, rehydrated, and subjected to heat-induced epitope retrieval. Sections will then be incubated with appropriate primary antibody. For signal detection, ultraView universal detection system (Ventana) will be used. The slides will be developed using 3-3'-diaminobenzidine chromogen and counterstained with hematoxylin. Appropriate positive and negative controls will be utilized for each run of immunostains. The evaluation of the immunostaining will be carried out by a genitourinary pathologist without knowledge of any clinicopathologic data. Only nuclear reactivity will be considered positive. An H score will be assigned as the product of average intensity of staining (0 for negative, 1 for weakly positive, 2 for moderately positive, and 3 for strongly positive) and extent of immunoexpression (0-100% percentage of cells staining). In addition, Dual-antibody ISH will be performed to identify and analyze TILs, CTL (CD3+,CD8+), Tregs (CD4+FoxP3), DC (CD11c) , NK/T (CD3+, CD1d), neutrophils (CD11b, Ly6G} and MDSC (CD14+,CD11b) in the tumor tissue before and after treatment, when available (see section 1.5).

9.2.7 **Serum Cytokine Analysis:** Multiplex cytokine analysis in patient's plasma will be performed in precoated 96 well plates (Human TH1/TH2 10 plex ultrasensitive assay, Meso Scale Discovery – MSD, Maryland, USA) according to manufacturer's instructions. 25 µL of diluent 2 is dispersed into each well. The plate is sealed and incubated by vigorous horizontal shaking for 30 minutes at RT.

25 µL of the patient plasma is added per well and all samples measured in

triplicates. Plates are sealed and incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS . 25 µL of 1× detection antibody solution is placed per well and sealed plates are incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS. 150 µL of 2× Read Buffer T is added to each well. Plates are analysed using the MSD SECTOR Imager 2400 and Discovery Workbench 3.0 software (both from Meso Scale Discovery, USA). The mean value of two wells is taken as the recorded reading, provided that the coefficient of variation (CV) was less than 10%. Concentrations recorded lower than the standard curve are kept as absolute values. For purposes of logarithmic analysis, readings of 0 are adjusted to 0.01 pg/ml. The following cytokines will be measured before and after treatment for each patients: Th1/Th2/Th17 cytokines, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, IL-17 TNF-α; pro-inflammatory cytokines: GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α; Chemokines: Eotaxin, MIP-1β, TARC, IP-10, IL-8, MCP-1, MCP-4 and others including IL-6, TGF-β and HMGB1 (see section 1.5).

9.2.8 **Western-blot/Immuno-blot:** LNCaP or PC3 human prostate cancer cell lysate will be used to perform immune-blott using plasma collected from patients before and after treatment. The LNCaP or PC3 cell 10^6 cells/mL will be lysed in immunoprecipitation assay buffer on ice for 30 min. Standard western blott methodology will be utilized. Briefly, 400 µg of protein will be separated using pre-made gradient 4% to 12% Bis-Tris gels (Invitrogen, Burlington, ON, Canada) and transferred to nitrocellulose. Patient sera/plasma will be diluted 1/500 in Blotto (5% dry milk powder; 0.1% Tween 20; 50 mmol/L Tris; 150 mmol/L NaCl) and incubated with nitrocellulose membranes for 1 h at room temperature using a multichannel immuoblotting device (Mini Protean II Multiscreen, Bio-Rad, Missassauga, ON, Canada). The membrane will then incubated for 1 h at room temperature with horseradish peroxidase–conjugated goat anti-human IgG (H+L; Jackson ImmunoResearch, West Grove, PA) diluted 1/10,000 in Blotto and visualized by enhanced chemiluminescence**.**

9.3 Specimen Banking

Subject samples collected for this study will be retained at the department of pathology and at the lab of Dr. Hannan. Specimen may be shipped to companies or outside institutions to perform specialized assays, a non-extensive list of which is provided above. Specimen will be shipped de-identified. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

Raquibul Hannan will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of UTSW.Any data obtained from the use of clinical specimen will be the property of UTSW for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UTSW, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 QUALITY OF LIFE AND COST-EFFECTIVENESS

10.1 Health-Related Quality of Life (HRQOL) Analysis

The study design is to prospectively analyze the HRQOL among patients with mCRPC treated with SABR and sipuleucel T. While hypofractionation is hypothesized to yield greater tumor cell kill, it may also increase the normal tissue toxicity, in which case there may be a decrease in HRQOL. The primary normal tissue toxicities in patients receiving radiation depend on the location of the treatment. Prior studies have demonstrated that the most sensitive and clinically meaningful method for accurately capturing the normal tissue toxicities is via patients reported outcomes (PROs), such as HRQOL.

In this non-randomized trial, we plan to assess the FACT-P at 3 specific time points to minimize patient burden: baseline (pretreatment), first follow up visit, and at one year (See Appendix). In order to analyze the QOL, we plan to use a brief, validated instrument that is user friendly and has clinical relevance [72]. FACT-G is a measure that sums the functional well-being (FWB), physical well-being (PWB), the social/family well-being (S/FWB), and emotional well-being(EMB). FACT-P adds to the FACT –G (27 items) by including 12 items specific to prostate cancer patients. The FACT-P has been validated as well and used in other studies evaluating treatment options for patients with mCRPC. It takes about 5-10minutes to complete and has been written at the 6th grade level. FACT has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org/translation/licensure.aspx.

In a HRQOL study focused on patient with advanced prostate cancer, the components of the FACT-P which showed a frequency greater than 17% were retained in a measure renamed the FACT Advanced Prostate Symptom Index -8 (FAPSI-8) [66]. Since pain was a major component of this simplified scale, we propose obtaining a Brief Pain Inventory to supplement the pain assessment of the FACT-P especially given the nature of this protocol likely accruing patients with minimally painful osseous metastases [73].

In addition, the EQ-5D and modified BPI HRQOL questionnaire will be used as well. EQ-5D is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The US version of the EQ-5D will be used, to enable mapping of general HR-QoL scores from EQ-5D scores into health state utility scores (ranging from 0 to 1) for the US population. These utility scores are needed for cost-utility analysis (estimates of costs per “quality adjusted” life-year gained) [74, 75].

HRQoL of patients with mCRPC is unfortunately not well described in the literature for either treatment modalities in this study or other standard of care treatments as well. [76].

A Canadian phase II study of docetaxel administered every 3 weeks with prednisone in men with metastatic hormone-refractory prostate cancer progressing after mitoxantrone/prednisone assessed quality of life as a secondary endpoint. A significant improvement (p=0.018) from 66 % pretreatment to 75% post 7 cycles of docetaxel was reported in the 30 patients treated on the trial [67]. The overall quality of life was maintained in these patients as well despite side effects associated with the treatment with docetaxel.

In another phase II study looking at mitoxantrone, estramustine, and vinorelbine (MEV) versus 13-cis retinoic acid (CRA), interferon-alpha2b (IFN), and paclitaxel (Tax) CRA/IFN/TAX, the patients treated in the CRA/IFN/TAX arm experienced a significant decrease in HRQOL as measured by the FACT-P [78]. This is one of the few studies that reports QoL in patients treated with mCRPC.

However, clearly, the lack of radiation given in the above mentioned studies and the various systemic treatments do not allow for the abovementioned studies to be appropriate comparisons for our study.

There is little reported on the effect on HRQOL for patients treated with Sipuleucel T, abiraterone, MDV3100, docetaxel, carbazitaxel, or other emerging treatment options for patients with mCRPC. Regarding the pain response to various treatment options for osseous metastases in the metastatic prostate cancer, there are innumerous reports [48]. Thus, we propose utilizing the FACT-P and a modified BPI questionnaire in the patients enrolled on this study for descriptive purposes as recommended in the PCWG2 [49]. .

Additionally, in order to calculate the indirect costs associated with hypofractionated radiation treatment, a single administration of a short economic questionnaire will take place at the first available follow up. This questionnaire which has been adopted for administration in the United States has been used in economic assessment in rural Canadian cancer health service research [79].

10.2 Cost-Effectiveness Analysis (CEA)

For the primary CEA analysis, we will estimate cost accumulated within 1 years. A larger limit is possible if we have a reasonable number of people surviving at that time.

Since patients are enrolled into the study over time and some patients are still alive at the end of the study, their survival time and costs are censored. Due to the presence censoring, we cannot use a simple average of the patients' total costs, a simple average of the patients' costs for those with complete cost information, or a Kaplan-Meier estimator on censored costs, since these all produce biased estimators of the mean costs[74]. Instead, we will use the inverse-probability weighting method to calculate average costs.[75, 80] The assumption used in this method is that censoring is independent of the survival time, or cost collection process, which is often satisfied in well-conducted clinical trials. If the new treatment can both extend patients' survival time (or quality-adjusted survival time), and save costs at the same time, the new treatment will be preferred to the current standard treatment under any willingness to pay threshold.

However, if the new treatment extends survival time but costs more, cost-effectiveness analysis provides an estimate of the incremental cost of greater incremental effectiveness. For traditional cost-effectiveness analysis, treatment effectiveness is measured simply as survival time. The incremental cost-effectiveness ratio indicates the additional cost required to attain one additional year of survival. For cost-utility analysis, treatment effectiveness is measured as quality-adjusted survival time (which accounts for the impact of treatment on both mortality and morbidity, including any differences in adverse affects of treatment affecting HR-QoL). For cost-utility analysis, the incremental cost-effectiveness ratio indicates the additional cost required to attain one additional year of quality adjusted survival.

10.2.1 Projection Model and Sensitivity Analysis

If the new treatment is implemented in usual practice, some of its potential benefits to patients may extend beyond the time horizon of the clinical trial. We will explore the potential to use results from the clinical trial based cost-effectiveness analysis, augmented with information from secondary sources, to develop a model to project costs and effectiveness beyond the time horizon included in the clinical trial. Any such model projections would be subjected to probabilistic sensitivity analysis, to assess the impact of parameter uncertainty on estimated cost effectiveness results. This is typically done via Markov Modeling with probabilistic sensitivity analysis.

10.3 Quality adjusted survival time:

The quality-adjusted survival time estimates need to account for the presence of censoring. Due to the induced informative censoring problem, the ordinary survival method (e.g., Kaplan-Meier estimator) cannot be applied in this case [75,80,81]. Accordingly, we will use the inverse-probability weighted method of Zhao and Tsiatis to carry out the survival time analysis [75, 80]. To estimate quality adjusted survival time, data from EQ-5D will first be translated into utility measures. These measures are obtained at discrete time points, so they will be interpolated into the time intervals between the visits. The quality-adjusted survival time is just an integration of the utility measures over a patient's survival time, or until the time limit similar as the cost calculation, whichever occurs earlier.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This is an open label phase II non-randomized single arm prospective clinical trial. The primary end point is TTP, while the secondary end points include improvement in immunologic response, PFS, bPFS, PCaSS, OS, quality of life and cost-effectiveness (Please see endpoint details in section 2 and 6)

11.2 Sample Size and Accrual

Sample size estimation is based on the assumption that Sipuleucel-T + SABR will improve the reported TTP with Sipuleucel-T alone by 80%. The TTP for Sipuleucel-T as reported by Kantoff et. al. is 14.6 weeks [10]. Assuming an 80% improvement would lead to a TTP of 26.28 weeks. According to the CRAB website (https://stattools.crab.org/Calculators/oneArmSurvivalColored.html), the estimated sample size with 2-sided test significance level of 10% and 80% power, assuming that the accrual time is 3 years, with a follow-up time of 4 years after the end of accrual, is 20. The secondary endpoints (i.e. OS, PFS etc.) will be followed for a total of four years. The estimated response rate using 20 patients can be measured with a maximum standard error of 11.2%.

11.3 Data Analyses Plans

This is a single-arm Phase II trial of SABR for mCRPC patients. TTP, OS, bPFS, PCaSS and duration of response will be estimated using the Kaplan-Meier approach along with the 95% confidence interval using Greenwood variance formula. Exact binomial method will be used to calculate the response rate and the corresponding 95% confidence interval. One-sample log-rank test [82] will be used to test if the survival endpoints such as TTP is significantly different from those in the historical control reported in Kantoff et. al [10].

Wilcoxon signed-rank test will be used to test if the median number of spots in Elispot of the PBMC collected from patients at 6, 14 and 26 weeks are at 100% increase in the median number of spots by ELISpot assay as reported in Sheikh et al [32]. T-Cell proliferation SI and ELISA antibody titer will also be evaluated in the same manner. Statistical analysis plans for cost-effectiveness and health-related quality adjusted life are described in Section 10.

12.0 STUDY MANAGEMENT

12.1 Conflict of Interest

12.2 Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW

Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

12.3 Required Documentation for multi-site

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office, Department of Radiation Oncology, UTSW.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

12.4 Registration Procedures

All subjects must be registered with the Clinical Research Office, Department of Radiation Oncology, UTSW, before enrollment to study.
New subjects will receive a 3-digit number. The first subject enrolled receives the number 101, the second subject enrolled receives the number 102, etc.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

12.5 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project. All subjects consenting to participate in any aspect of the trial must be registered on REDCap before initiating protocol activities. All research data will be recorded and entered into Case Report Forms using REDCap.

Toxicity will be reviewed on an ongoing basis and will be reported per SCCC-DSMC guidelines.

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

Clinical trials are assessed for safety on a continual basis throughout the life of the trial. All SAE's and any AEs that are unexpected and possibly/likely related to study participation are reported to UTSW IRB through an electronic research system per UTSW IRB guidelines. SAEs are reported to the sponsor per specific sponsor requirements. These SAEs are reported to the SCCC DSMC on a real time basis. All local SAEs will be reported to the SCCC DSMC. SAE reports can be either scanned/emailed to the coordinator of SCCC DSMC or sent through interoffice mail.

RADIATION ONCOLOGY DATA SAFETY MONITORING PLAN

1. The purpose of the Radiation Oncology Data and Safety Monitoring Plan is to ensure that clinical trial data is accurate and valid and to ensure the safety of trial participants. The plan complies with the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Plan and the University of Texas Southwestern Medical Center (UTSW) IRB guidelines.

2. The Radiation Oncology Safety Assurance Committee (ROSAC) is charged with developing, implementing, and maintaining the Data and Safety Monitoring Plan. The membership consists of a Medical Director of Clinical Research as well as representation from the following groups: clinical research, nursing, regulatory,

pharmacy, physicists, radiation therapists, and faculty. Ad hoc members are contacted to participate as needed.

3. Clinical trials are assessed for safety on a continual basis throughout the life of the trial. Serious Adverse Effects (SAEs) and any Adverse Effects (AEs) that are unexpected and possibly/likely related to study participation are reported to UTSW IRB through an electronic research system per UTSW IRB guidelines. SAEs are reported to the sponsor per specific sponsor requirements. All SAEs are reported to the SCCC DSMC on a real time basis. SAE reports can be either scanned/emailed to the coordinator of SCCC DSMC or sent through interoffice email.

4. All clinical trials are reviewed by ROSAC on a monthly basis for enrollment. All local SAEs are reviewed by ROSAC monthly for severity and attribution. For investigator-initiated trials, SAEs at affiliated institutions are monitored as local SAEs. The principle investigator and study coordinator will present a study treatment summary and SAEs for review. Source documents will be available for the ROSAC members during the review. NCI Common Toxicity Criteria Version 4 will be used for grading and attributing adverse events. The documentation of these monthly reviews will be submitted to the SCCC DSMC on a monthly basis.

5. If a related SAE occurs on a multi-institutional clinical trial coordinated by the Radiation Oncology Clinical Research Office, the Clinical Research Manager or designee ensures that all participating sites are notified of the event and resulting action, within one (1) working day of the determination.

6. All participating sites will be monitored annually. At least 5 charts for each site will be reviewed each time a site is monitored. Monitoring will include verification of source documentation as per SCCC DSMC plan. Results of data monitoring along with any necessary responses, if applicable, will be documented and filed within the Department of Radiation Oncology. These documents are available upon request at time of audit. All monitoring will be performed remotely, however on-site visits may be scheduled as necessary per DSMC policy.

12.6 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

12.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

12.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

➢ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

12.6.3 Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

12.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

12.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an

International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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14.0 APPENDICES

14.1 Appendix A: ECOG Performance Status

ECOG/ZUBROD PERFORMANCE SCALE

0	*Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).*
1	*Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).*
2	*Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).*
3	*Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).*
4	*Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).*
5	*Death (Karnofsky 0).*

KARNOFSKY PERFORMANCE SCALE

100	*Normal; no complaints; no evidence of disease*
90	*Able to carry on normal activity; minor signs or symptoms of disease*
80	*Normal activity with effort; some sign or symptoms of disease*
70	*Cares for self; unable to carry on normal activity or do active work*
60	*Requires occasional assistance, but is able to care for most personal needs*
50	*Requires considerable assistance and frequent medical care*
40	*Disabled; requires special care and assistance*
30	*Severely disabled; hospitalization is indicated, although death not imminent*
20	*Very sick; hospitalization necessary; active support treatment is necessary*
10	*Moribund; fatal processes progressing rapidly*
0	*Dead*

14.2 Appendix C: FACT-P

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

14.3 Appendix D: EQ-5D

(English version for the USA)

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑

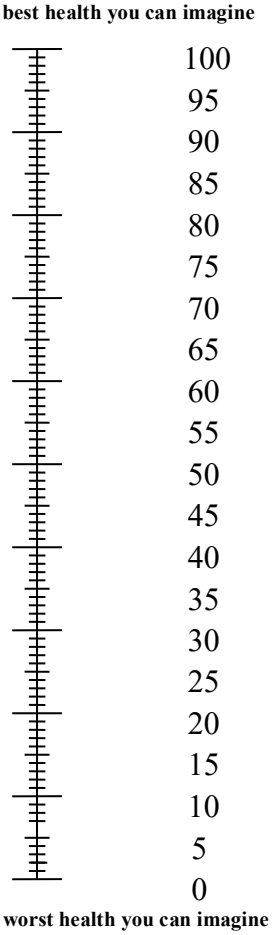
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



14.4 Appendix E: BPI

Brief Pain Inventory

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

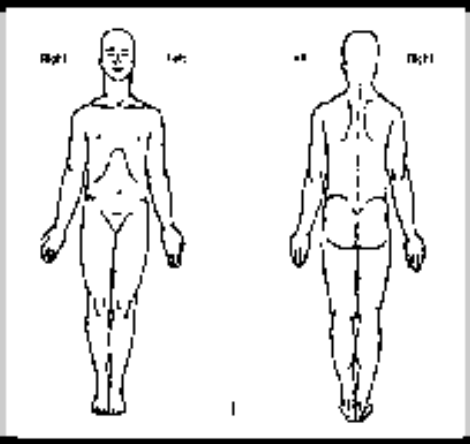
Name: _____ _____ _____

Last First Middle Initial

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

   1. Yes 2. No

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



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

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

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

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

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

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

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

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

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

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

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

14.5 Appendix F – Patient Perspective Cost and Convenience of Care Questionnaire

We would like to ask you about your health coverage and the "out-of-pocket" costs you have had related to your cancer treatment.

1. Do you have any coverage that helps pay for your medicines, when you are **NOT** in the hospital: (Check **ALL** that apply)

   ❑ **Yes by Government (e.g. ,Medicare Part D,Tricare, etc.)**

   ❑ **Yes by private or employer-paid health insurance (supplemental)**

   ❑ **No coverage**

   ❑ Don't Know

2. Do you have any coverage that helps pay for home or community care, when you are **NOT** in the hospital (i.e. nursing, physiotherapy, cleaning, etc.): (Check **ALL** that apply)
   - ❑ Yes by Government (Medicare, Medicaid, Tricare)
   - ❑ Yes by private or employer-paid health insurance
   - ❑ No coverage
   - ❑ Don't Know

If you do NOT have private or employer paid health insurance ☞Go to Question 4

TYPE OF SERVICE	✓*Don't Know*	✓*Not Covered*	✓**Partial Coverage**	✓**Full Coverage**
Hospital supplemental charges (e.g. Private room, telephone, TV, etc.)				
Prescription drugs (e.g. Antibiotics, pain medication, etc.)				
In home healthcare (e.g. nursing, physiotherapist, etc.)				
Homemaking services (e.g. cleaning, cooking, etc.)				
Alternate Therapy (e.g. Homeopathy, Chinese medicine, over the counter drugs, etc.)				
Other (Specify) _____ _____				

3. If you have Private/Employer-paid health insurance, please describe your coverage for each type of service: (For each service, check the box that best describes your level of coverage.)

☞**Proceed to Question 4**

4. Please supply the following details regarding your "out-of-pocket" costs for trips to and from your treatments and family doctor visits **related to your cancer** *in the last 30 days*.

Type of Visit	**Number of trips in the last 30 days**	**Distance <u>ONE WAY</u> OR** origin and destination points	**Method of transport (car, taxi, bus, train etc.)**	**Parking or Fare**	**Paid for by Insurance/ Government (circle one)**
Cancer Clinic/ Radiation Facility		Miles		$	None – Partial - Full
Hospital		Miles		$	None – Partial - Full
Family Doctor		Miles		$	None – Partial - Full
Other (Specify, i.e. 2nd Hospital or 2nd Doctor, ER) _____		Miles		$	None – Partial - Full

5. For questions listed below indicate if you had cancer related costs, paid by yourself, private insurance or government programs (e.g. Home Oxygen, Homecare, etc.) *during the last 30 days*. If you do not know the exact amount make your **best estimate,** rounded to the nearest dollar.

a) **Copays**

❑ No	❑ Yes (Check all that apply and fill in related estimate of dollar amount)		
	❑ paid by yourself Amount (if known): $ _____	❑ paid by private insurance N/A	❑ paid by government N/A

b) **Prescription Drugs**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

c) **In home healthcare (nursing, physical therapy, respiratory therapy, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

d) **Homemaking (cleaning, cooking, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

e) **Complementary and Alternative Therapy (homeopathy, massage, acupuncture, counseling, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

f) **Vitamins and Supplements including special diets**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

g) **Family Care (child or elder)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

h) **Accommodation/Meals**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

i) **Devices or Equipment (<u>home oxygen</u>, wheelchair, walker, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself Amount (if known): $ _____

❑ paid by private insurance $ _____

❑ paid by government $ _____

j) **Other (telephone costs, pagers, etc..)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)

❑ paid by yourself ❑ paid by private insurance ❑ paid by government

Amount (if known):

$ _____ $ _____ $ _____

6. Would you say this last month your "out-of-pocket" expenses related to your cancer were:

❑ More than other months ❑ Typical ❑ Less than other months ❑ Don't Know

We would like to ask you some questions about your healthcare visits related to this cancer as well as the impact these visits have had on your work.

7. Since you finished radiation, have you had: (Check all that apply)
NOTE: We will ask you specific questions about these in a separate form.

❑ Doctor visits
❑ Emergency room visits
❑ Overnight hospitalization – indicate duration ❑ one or _____ nights.
❑ Home nursing services
❑ Respiratory/ Physiotherapists/ Occupational Therapy services
❑ Medication changes
❑ Started oxygen treatment

8. How much time over the *last 30 days* did you take off work to receive treatment related to your cancer

❑ Unemployed ❑ No time off work ❑ _____ days ❑ Don't Know
❑ Retired

9. Was this time away from work: (Check ALL that apply)

❑ Not Applicable (not working) ❑ Vacation ❑ Time off **with** pay ❑ Time off **without** pay

10. Did friends or family take time away from work in the *last 30 days* related to your treatment

❑ No time off work **OR** ❑ _____ days

We would now like to ask you a little bit about you, your work and your education:

11. Year of Birth _____

12. Sex: ❑ Male ❑ Female

13. Marital Status:

❑ Married ❑ Common Law ❑ Single (never married)
❑ Widowed ❑ Separated ❑ Divorced

14. How many other people do you share your home with (do not include people who are only visiting):

❑ Live alone (□ **Go to Question 16**) ❑ Myself and one other
❑ 2 others ❑ 3 others ❑ More than 3 others

15. Are these people you share your home with:

❑ Family ❑ Friends ❑ Both Family and Friends

16. City or Town where you live _____

17. How would you rate your current health?

❑ **Excellent** ❑ **Very good** ❑ **Good** ❑ **Fair** ❑ **Poor**

18. What do you do for a living:

❑ *Full time work : Specify* _____ ❑*Part time work: Specify* _____
❑ *Retired* ❑ *Homemaker* ❑ *Unemployed* ❑ *Student*

19. What is the highest level of schooling you have completed?

- ❑ No schooling, some elementary school, or completed elementary school
- ❑ Some high school
- ❑ Completed high school
- ❑ Some university or community college
- ❑ Completed university or community college
- ❑ Post Graduate (MSc/MBA/PhD) or professional training (MD/LLB/DDS)

20. What was your total family income before taxes in the last year.
(include wages, salaries and self-employment earnings)

- ❑Less than $5,000
- ❑$5,000- $9,999
- ❑$10,000- $14,999
- ❑$15,000- $19,999
- ❑$20,000-$29,999
- ❑$30,000-$39,999
- ❑$40,000-$49,999
- ❑$50,000-$59,999
- ❑$60,000-$79,999
- ❑More than $80,000
- ❑Don't Know

21. How much of a financial burden are these out-of-pocket expenses listed in Q 4 & 5:

- ❑Not a burden at all
- ❑Only a slight burden
- ❑Somewhat of a burden
- ❑Significant burden, but manageable
- ❑Unmanageable burden

24. What treatments or services that are **not** currently available would you like to see paid for through government or private insurance:

_____

_____

25. Was this questionnaire completed by:

❑ The patient ❑ A caregiver ❑ Both the patient and a caregiver

We would like to learn more about your personal reactions to the treatment and the impact it had on your typical activities:

26. To what extent has your treatment **disrupted** your normal daily activities?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

27. To what extent has your treatment **disrupted** your normal recreation activities?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

28. To what extent has your treatment **disrupted** your normal activities with your family and friends?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

29. To what extent has your treatment **disrupted** your sleep pattern?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

30. To what extent has your treatment **disrupted** your enjoyment of life?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

31. How **satisfied** are you with the length of time your treatment has taken to this point of time?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

32. How **disruptive** has your treatment been to the other important people in your life (example: family, spouse, close friends, coworkers)?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

Additional Comments

_____
_____
_____
_____-
_____

Thank you *for helping us with our survey. If you have completed all sections please place the survey in the envelope, seal it, and return it to the attending clinic staff. Retain the information sheet.*