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Phase 2 Clinical Trial of Stereotactic Radiotherapy and PD-1 or PD-L1 Inhibiting Therapy for Treatment of Advanced Solid Tumors After Disease Control on PD-1 or PD-L1 Inhibiting Therapy
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Virginia Commonwealth University Massey Cancer Center

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Phase 2 Clinical Trial of Stereotactic Radiotherapy and PD-1 or PD-L1 Inhibiting Therapy for Treatment of Advanced Solid Tumors After Disease Control on PD-1 or PD-L1 Inhibiting Therapy

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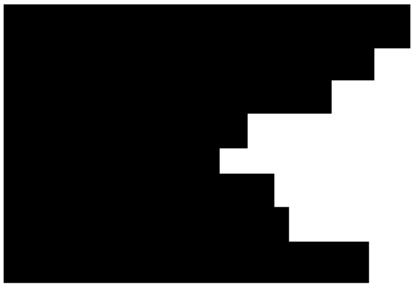

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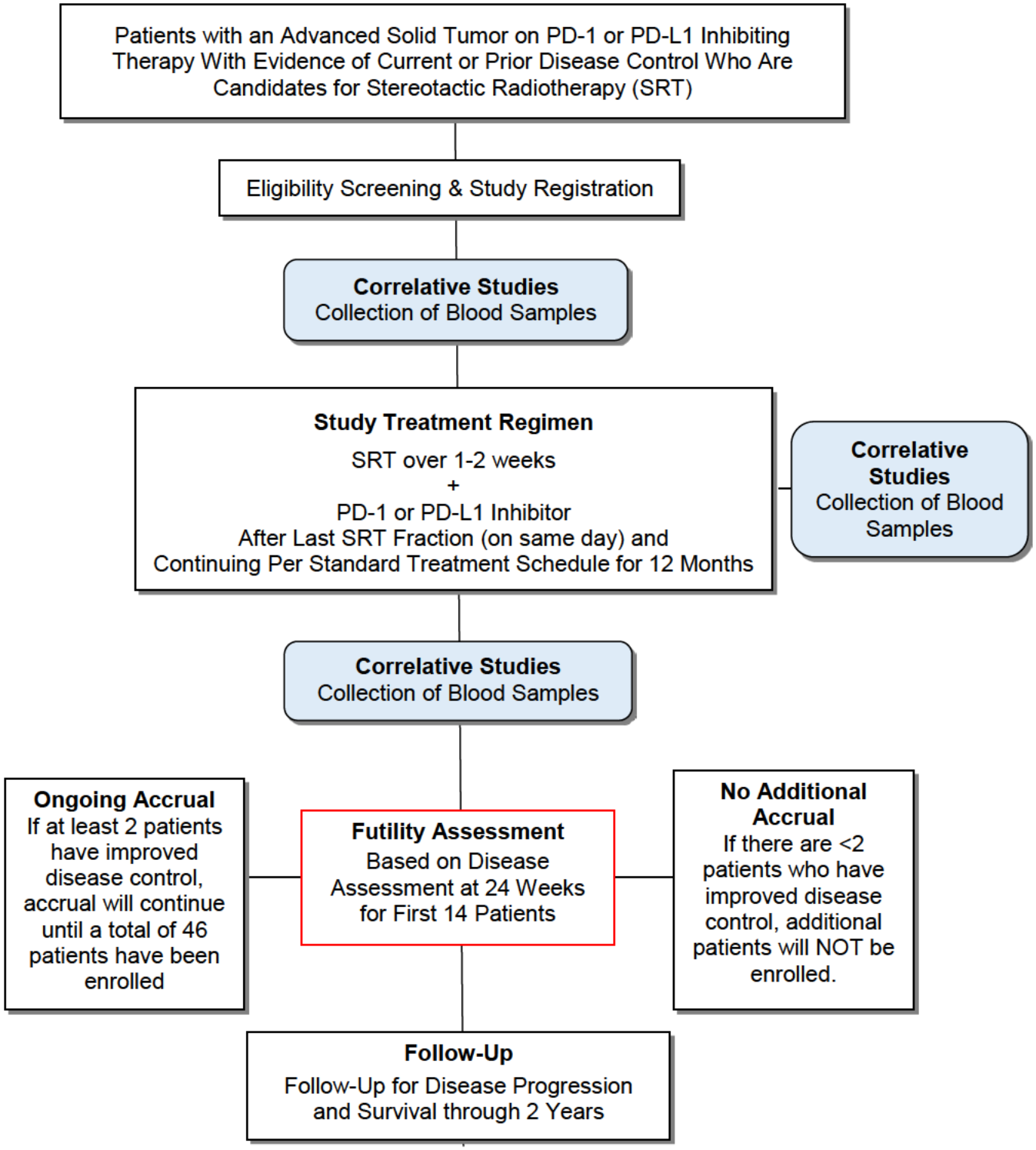
LIST OF ABBREVIATIONS

AE	adverse event
CBC	complete blood count
CNS	central nervous system
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated protein 4
DSMC	Data and Safety Monitoring Committee
eCRF	electronic case report form
FDA	Food and Drug Administration
GTV	gross tumor volume
Gy	gray
IIT	investigator-initiated trial
irAE	immune-related adverse event
iRANO	immunotherapy Response Assessment in Neuro-Oncology
irRC	immune-related response criteria
IRB	Institutional Review Board
ITV	Internal tumor volume
MCC	Massey Cancer Center
NCI	National Cancer Institute
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand 1
PR	partial response
PRMC	Protocol Review and Monitoring Committee
PTV	planning target volume
RANO-BM	Response Assessment in Neuro-Oncology for Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiation therapy
SAE	serious adverse event
SBRT	stereotactic body radiotherapy
SD	stable disease
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
TRegs	regulatory T cells
UP	unanticipated problem
VCU	Virginia Commonwealth University
WCBP	woman of childbearing potential

STUDY SCHEMA



1 BACKGROUND

1.1 Radiotherapy and the Abscopal Effect

The immune system distinguishes “self” from “non-self,” and targets “non-self” for elimination. This process forms the basis of our immunity to pathogens and the primary barrier to organ transplantation. Cancer, however, is neither “self” nor “non-self,” but rather “altered-self” and evades detection and elimination by the immune system through multiple mechanisms. The ultimate goal of cancer immunotherapy is to target and reverse these tumor-induced immunosuppressive processes, allowing the activated immune system to eradicate the cancer and develop immunologic memory to combat future recurrences before they become clinically apparent (1).

Radiotherapy has been a primary oncologic therapeutic modality for approximately a century, and it was recognized prior to 1950 that in rare circumstances, radiation of a single tumor resulted in regression of not only the irradiated tumor, but also regression of distant tumors not irradiated. This phenomenon was termed “The Abscopal Effect.” Contemporary preclinical work from various tumor immunology groups have demonstrated that the abscopal effect is mediated by the immune system (2, 3).

1.2 Biologic Rationale for Combining Immunotherapy and Stereotactic Radiotherapy

Stereotactic radiotherapy (SRT), in which large radiation doses per fraction are given, has been combined with immunotherapy to potentiate the abscopal effect of radiotherapy (1). A recent review describes the biologic rationale for combining immunotherapy and SRT. Tumor cells can downregulate major histocompatibility complex I (MHC I) expression to avoid immune system detection (4). One possible mechanism of the abscopal effect of radiation is upregulation of MHC I expression after radiation, which eliminates tumor cells’ ability to evade immune detection via this pathway (3, 5, 6). Radiation also increases the quantity of tumor-specific antigens for immune presentation (7). However, upregulation of MHC I expression and increased antigen supply are insufficient – activated T cells must be present to recognize and kill the tumor cells (1, 6).

Both cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors, by keeping T cells activated for longer periods, and programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors, by preventing apoptosis of T cells, can potentiate the abscopal effect of radiotherapy. However, a documented mechanism of tumor resistance to CTLA-4 inhibition is upregulation of PD-1 activity (8). Preclinical work has shown that PD-1 activity can moderate the abscopal effect of radiation therapy (9, 10), and that tumors can increase PD-1 activity after radiotherapy (11). Correspondingly, a documented mechanism of tumor resistance to PD-1 inhibition is downregulation of MHC I expression (1). Therefore, the combination of SRT and PD-1 inhibiting therapy may offer enhanced tumor responses by disrupting known resistance mechanism to both individual therapies.

In murine models, the combination of immune checkpoint inhibitors and SRT generated more robust treatment responses than either individually (9, 11-15). In murine melanoma and mammary carcinoma models, SRT augmented the response of combined PD-1 and CTLA-4 inhibition, even in cell lines previously resistant to CTLA-4 inhibition (8).

1.3 Clinical Experience with Immunotherapy and Stereotactic Radiotherapy

Within the past 5 years, immune checkpoint inhibitors such as nivolumab and pembrolizumab (PD-1 inhibitors), atezolizumab and durvalumab (PD-L1 inhibitors), and ipilimumab (a CTLA-4 inhibitor) have demonstrated improved outcomes in patients with advanced solid tumors, first in melanoma (16-21) and subsequently in non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of head and neck (SCCHN), and bladder cancer (22-36), among others, leading to approval by the US Food and Drug Administration (FDA) for their use in these cancers with additional indications expected in the near future.

Despite these dramatic improvements in patient outcomes, the majority of cancers progress on PD-1 and PD-L1 inhibitors, leaving them few options for treatment. While conventional thinking suggests that there is no further role for re-use of cytotoxic therapy or targeted therapy once tumors are resistant to those agents, immune checkpoint inhibitors may be different. As these agents do not target the tumor directly, the immune system may be more dynamic, and there may be modulations that can allow immune checkpoint inhibition to gain tumor control following initial progression while on these agents. Formal exploration of re-treatment strategies could begin to shed light on this process, and open new opportunities for therapy.

Multiple groups have published case reports of patients who were failing immune checkpoint immunotherapy until they received SRT to a single lesion, after which regression of the irradiated lesion as well as lesions outside of the radiation field with attendant changes in molecular markers of immune activation was observed (1, 37, 38). Similarly, radiotherapy to oligo-progressive metastatic lesions has been shown to prolong the efficacy of tyrosine kinase inhibitors in lung cancer (39, 40). These reports have fueled a growing area of clinical investigation into the combination of radiotherapy and immunotherapy.

1.4 Rationale for PD-1 and PD-L1 Inhibitors Versus CTLA-4 Inhibitors

The efficacy of PD-1 inhibition versus CTLA-4 inhibition has rarely been directly evaluated. PD-1 inhibitors have been shown to be effective in patients with melanoma that has previously progressed on ipilimumab (41-43). In a three-arm phase 3 trial comparing ipilimumab (a CTLA-4 inhibitor), nivolumab (a PD-1 inhibitor), and dual immune therapy in treatment-naïve patients with unresectable or metastatic melanoma, nivolumab demonstrated superior response rates and progression-free survival compared to ipilimumab (44). These results were replicated with pembrolizumab compared to ipilimumab (45).

PD-1/PD-L1 inhibition and CTLA-4 inhibition target distinct pathways and have different mechanisms of action (46). Since PD-1 pathway inhibition has demonstrated superior response to CTLA-4 inhibition in melanoma (18, 44) and has proven effective in multiple cancer histologies after progression on CTLA-4 inhibition (8, 41-43), we have decided to pursue the combination of PD-1 or PD-L1 inhibiting therapy and SRT rather than CTLA-4 inhibiting therapy and SRT. The toxicity profile of PD-1 inhibition appears to be more favorable than that of CTLA-4 inhibition (44). Should our initial study demonstrate favorable outcomes, then the combination of SRT and dual immune therapy could be evaluated in a subsequent study, given the excellent responses of dual immune therapy seen in melanoma.

Although both classes of immune therapy have approval in melanoma, PD-1 inhibitors have FDA approval for use in NSCLC, RCC, and SCCHN, with additional indications expected in the near future. Also, the PD-L1 inhibitor, atezolizumab, has been approved by the FDA for

treatment of metastatic urothelial carcinoma, with additional indications expected in the near future. Therefore, the use of PD-1 and PD-L1 inhibitors, instead of CTLA-4 inhibitors, expands the eligible population now in this study and in the future.

1.5 Inclusion of Multiple Advanced Solid Tumors

PD-1/PD-L1 inhibiting therapy has demonstrated efficacy in multiple tumor types. Similarly, the abscopal effect has been seen in multiple tumor types (47-57). By limiting our population to patients who have demonstrated disease control on PD-1 or PD-L1 inhibiting therapy, we select patients with tumors that have the highest likelihood of responding to further immune modulation with radiotherapy and continued immunotherapy. This population is also consistent with the patients described in case reports of combining SRT and immunotherapy. Our plans for statistical methodology that includes both overall and disease-specific futility assessments increases the likelihood of identifying tumor types that respond to combination therapy.

1.6 Inclusion of Brain Metastases

While patients with brain metastases were excluded from most of the seminal studies leading to the adoption of PD-1 and PD-L1 inhibiting therapy, PD-1 inhibitors have demonstrated efficacy in brain metastases (58, 59), and the combination of SRT and PD-1 inhibitors in the treatment of brain metastases has been shown to be safe (60, 61). Additionally, the reduced blood brain barrier seen in brain metastases suggests that radiotherapy to these lesions offers a similar, if not identical, chance for immune reactivation compared to radiotherapy to extracranial sites (62).

Our radiation oncology group is not comfortable with observing intracranial disease given the potential for these lesions to quickly cause debility and/or death. Therefore, patients with brain metastases will be included in this study provided all brain lesions can be treated with SRT and there is extracranial measurable disease that can be observed. Given the limited data on the immunogenicity of brain metastases, enrollment of patients who receive SRT to brain metastases alone will be limited and their data analyzed separately.

1.7 Opportunity for Novel Investigation

Most of the recent clinical trials evaluating the combination of SRT and immunotherapy are enrolling patients who are naïve to immunotherapy, and recently published studies in melanoma, prostate cancer, and other solid malignancies investigated immunotherapy-naïve patients (8, 63-65). However, in the seminal case report detailing the abscopal effect in a patient with metastatic melanoma, the patient, who had previously responded to ipilimumab but was progressing on immunotherapy, received SRT to a painful paraspinal metastasis while continuing immunotherapy (37).

To date, no studies have prospectively examined combination therapy in patients with tumors that have progressed on prior immune checkpoint inhibiting therapy, recreating the conditions described in prior case reports. In this clinical trial, SRT and immunotherapy will be combined to treat patients who have had disease control from immunotherapy but did not continue to improve.

1.8 Volumetric Measurements for Response Assessment

Most criteria for evaluating treatment response use unidirectional or 2-dimensional tumor measurements to assess response. In this study, the feasibility of using volumetric measurements of tumor size will be explored.

1.9 Evaluation of Immunologic Correlates Using Blood Samples

1.9.1 Significance and Background

The mechanisms underlying radiation therapy (RT)-induced antitumor immune responses are complex, but are likely related to secretion of certain immunostimulatory cytokines and chemokines, systemic immune response against tumor antigens, systemic signaling by exosomes released from tumor cells, and local inflammation contributing to a distant effect (66). For example, serum IFN-γ levels were found to increase in a dose-dependent fashion in patients with esophageal squamous cell carcinoma who were treated with RT alone. Type I interferons (IFN-α and IFN-β) not only play important roles in the immune responses to viral infection, but are also actively involved in antitumor immunity (67). RT can induce production of Type I interferons through activation of intracellular DNA sensors, such as the STING-dependent pathway (68, 69). Induction of Type I interferon within the TME is required for generation of Type I interferon-dependent innate and adaptive antitumor immunity by potentiating the cross-priming capacity of tumor-infiltrating antigen-presenting cells, such as dendritic cells, as well as recruitment and effector function of $CD8^+$ T effector cells (70, 71).

Exosomes are small (30–150 nm) vesicles containing unique RNA and protein cargo, secreted by all cell types in culture. They are also found in abundance in body fluids including blood, saliva, and urine (72-74). Interest towards exosomes, from their function in the body to more practical applications, such as the use in diagnostics (based on analysis of their miRNA and protein content) and therapeutics development, has grown exponentially in the last 5 years (75). With the current advances the analysis of exosomal miRNA from biological samples such as blood is more feasible than ever before. Furthermore, the cargo contained in exosomes provides an enriched population of miRNA free of endogenous RNA contaminants such as ribosomal RNA (rRNA). Therefore, these exosomes contains a disease-specific miRNA signature, which is very attractive for diagnostic purposes (76-78).

Investigators have also examined the interactions of cancer-derived exosomes with primary T-lymphocytes (79-82). For example, previous studies have demonstrated that these cancer-derived exosomes induce apoptosis in CD8+ T-lymphocytes through the FAS/FASL pathway. Other studies have demonstrated that tumor-derived exosomes up-regulate expression of inhibitory genes in conventional CD4+T cells and their conversion into CD4+ CD25high FOXP3+ CD39+ Treg (83, 84), which co-expressed IL-10 and TGF-β, CTLA-4, granzyme B/perforin and effectively mediated immune suppression.

RT can also induce extensive immunogenic alterations of dying and surviving cancer cells within the tumor microenvironment. The resulting stress and death of tumor cells could stimulate tumor-specific immune responses through the liberation of ‘danger’ signals or damage-associated molecular patterns, together with tumor-associated

antigens. Specialized antigen-presenting cells can capture tumor antigens and concurrently activate the 'danger' signals by engaging their corresponding pattern recognition receptors, such as toll-like receptors on the surface of immune cells (85, 86). The resultant antigen presentation can potentially lead to recruitment and priming of T cells and consequent immune-mediated destruction of tumors and/or metastases (87).

1.9.2 Preliminary Studies

The VCU Department of Radiation Oncology has an ongoing blood draw study (HM-12181) collecting blood samples from patients receiving RT with curative intent for cancer of the thorax (lung, breast, prostate, rectal, cervical, head and neck). We have published a preliminary analysis of retrospective patient blood samples collected for single-nucleotide polymorphisms (SNPs) in genes encoding HO-1, eNOS, NRF2 and TGF-β1 (87). NRF2 is a transcription factor for HO-1 expression and NRF2 knock-out mice are sensitive to radiation-induced lung injury (88). We also analyzed position -509 in the promoter of TGF-β1 because the minor allele is associated with enhanced promoter activity and TGF-β1 expression and previous studies had generated conflicting results of whether the minor allele was predictive for the late effects of radiotherapy. This study showed that polymorphisms of 3 genes involved in wound repair and response to radiation potentially predicted late normal tissue toxicity if racial differences in polymorphism frequencies are considered. Increased frequency of a long GT repeat in the promoter was associated with late effects in both African-Americans and Caucasian patient populations. SNPs in the TGFβ1 and NRF2 promoters were significantly associated with late effects in African-Americans but not Caucasians. These latter findings demonstrate that the demographics of the VCU patient population and tissue bank will allow us to test for racial differences in the response of tissues to radiation.

In a preliminary study (Serrano et al, in preparation), exosomes were isolated from the plasma of patients with lung cancer on HM12181 the day before RT started, 3 weeks into RT and 6 months after the end of treatment (Figure 1). Exosomes from patients with recurrence isolated 6 months post-RT recovered their growth-promoting property in contrast to exosomes from patients who demonstrated no tumor recurrence. These results suggest the potential for exosomal biomarkers of tumor recurrence after therapy.

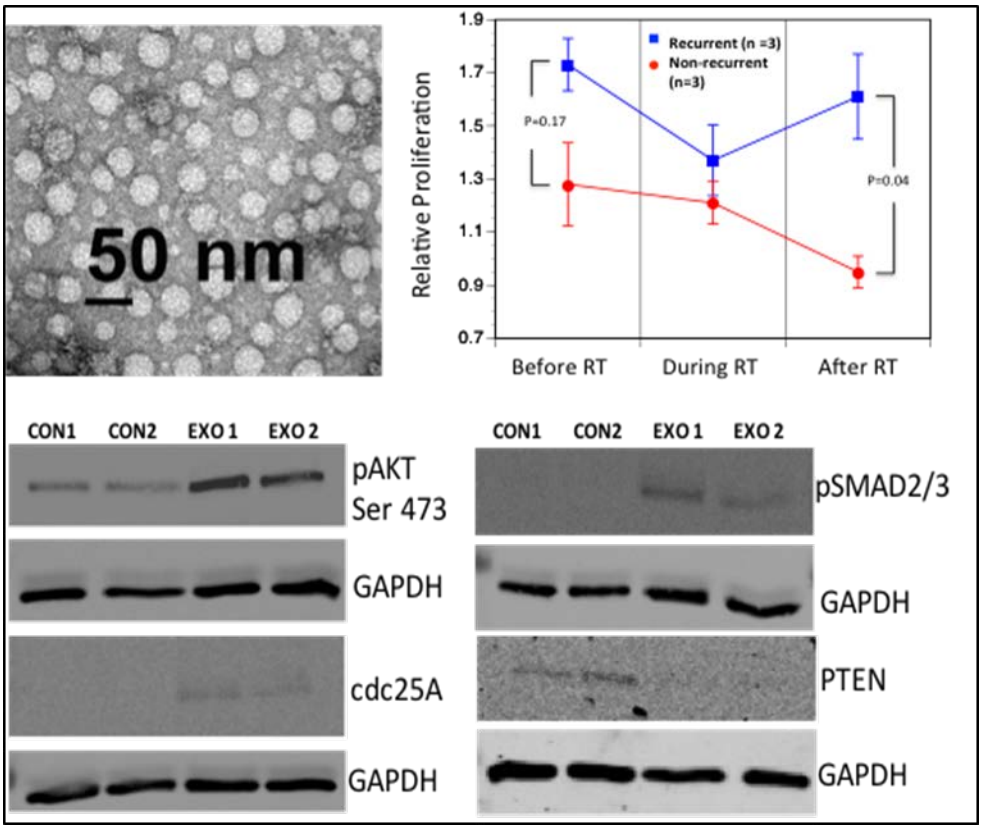


Figure 1. Exosomes Isolated from the Plasma of Patients with Lung Cancer Stimulate Fibroblast Proliferation

The relative expression levels of 10 different miRs selected on the basis of their roles in lung cancer were also determined: let-7a-5p, miR-20a-5p, miR-21-5p, miR-30b-5p, miR-106a-5p, miR-146a-5p, miR-155-5p, miR-200b-5p, miR-203a, and miR-208a-5p. Expression of 6 miRs demonstrated significant difference between recurrent and non-recurrent groups of lung cancer patients (Figure 2). Results are shown as an average of miRs expression (Cq-values) for recurrent (3 patients) and non-recurrent (3 patients) lung cancer before, during, and 6 months after therapy. Given the exponential property of Cq, the differences observed between the recurrent and non-recurrent patients are orders of magnitude. The Cq-values were normalized with respect to plasma volume. If the Cq-values are converted into fold differences, there is a significant difference between miR expression before and after therapy in the non-recurrent group (eg, let-7a demonstrates >5-fold decrease, miR-21 demonstrates >10-fold decrease). miR-155 is most probably absent at all time points in the non-recurrent group. When plasma exosome concentration numbers are determined, patients in the non-recurrent group consistently demonstrated only 3- to 5-fold decrease of exosome concentrations suggesting that the tumor cell is not an exclusive source of these exosomes, at least at 6 months post-therapy.

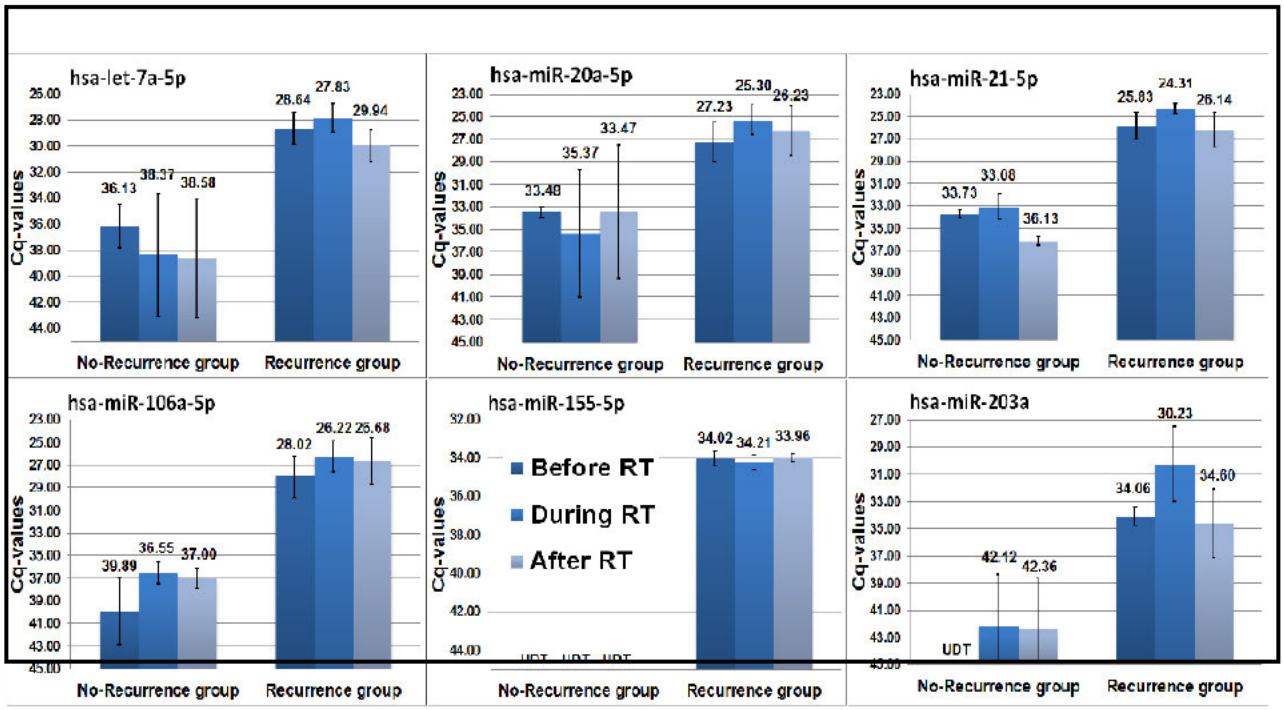


Figure 2. miR Analysis of Plasma Exosomes from Patients with Lung Cancer Normalized to Plasma Volume Extracted

qRT-PCR analysis of miR expression in exosomes isolated from the same patients as those in Figure 1. Exosomal miRs were purified with kits from Norgen and, as discussed in the text, 10 miRs were analyzed. Additionally, two RNA spike-in controls were used: UniSp6 as the cDNA synthesis control, and UniSp3 as the interplate calibrator. Cq – quantification cycle; UDT – Cq undetermined after 45 cycles.

1.9.3 Biological Objectives

We will conduct correlative immunologic endpoints within each patient pre- to post-therapy and across the cohort of patients to elucidate the mechanistic immunologic effects of therapy. Blood samples will be obtained from patients prior to initiating SRT, prior to the second fraction of SRT, at the end of SRT, and at 8, 24, and 52 weeks post-SRT.

De-identified blood samples will be processed to collect buffy coat. Immune monitoring of blood samples will be performed on samples collected from all patients longitudinally throughout the study. Analytical flow cytometry will be performed to enumerate the frequencies of immune cell populations, including CD8+ T cells, regulatory T cells (Treg, CD4+Foxp3+), and CD11b+CD14-CD33+ myeloid-derived suppressor cells (MDSCs). Immune cell functional status will be determined by combinational staining of markers for T-cell activation (perforin, granzyme B, CD69, and CD107) and exhaustion (PD-1, LAG-3, TIM-3, and CD244). DNA will be prepared from the buffy coat and subjected to qPCR evaluation of the expression of immune-related genes for example: T-cell activation-related cytokines (IFN-γ), immunosuppressive enzymes, and molecules (IDO, arginase, CTLA-4, PD-1/PD-L1).

Exosomes will be isolated from plasma using the Norgen kit (Figure 1) and quantified by acetylcholinesterase activity and protein. From 1.0 mL plasma we isolate between

0.7 and 3.0 mg exosomal protein and 6-12 ng exosomal miR depending on the patient and time point. Quality and quantity of miR are assessed using a bioanalyzer and an Agilent small RNA chip and kit. Protein and miR are sequentially isolated from exosomes using the Norgen kit. From our prior experience, for example in Figure 1, we obtain sufficient amounts of exosomes from individuals to perform the proposed analyses, eg amount of exosomal miRs extracted from 0.7mL of serum is enough for at least 30,000 qPCR reactions. qRT-PCR is the gold standard for miR measurement.

For functional analysis of exosomes, we will determine whether exosomes isolated from cancer patients as described above induce apoptosis of activated CD8+ T cells isolated from anonymized blood samples purchased from a local blood bank (79-82). Additional experiments will test whether tumor-derived exosomes mediate immune suppression by stimulating proliferation of conventional CD4+ T cells and their conversion to CD4+CD25highFoxP3+CD39+ Treg cells expressing IL-10, TGFβ, CTLA-4, and granzymeB/perforin (83, 84). Experiments described above in Figure 1 evaluating whether exosomes stimulate fibroblast proliferation will be continued.

1.10 Rationale for Inclusion of Patients with Stable Disease

SRT is often used clinically in individuals who have not had progression of disease, but who may still benefit from radiation. Some situations when this would be appropriate include but are not limited to:

- Metastatic sites that, if left to grow, would cause clinical issues but are currently asymptomatic, such as spinal metastases that could cause cord compression
- Metastatic sites that are causing symptoms such as pain, neurological changes, shortness of breath, hemoptysis, or rectal bleeding
- Oligoprogressive metastasis in which most of the metastatic sites have responded to immunotherapy but one or more has grown larger.

Recent studies indicate that the combination of the immunotherapy drugs and SRT is well tolerated, with toxicity similar to monotherapy (89-91). Preliminary results also indicate the presence of abscopal response in non-irradiated measurable lesions with concurrent pembrolizumab(90). Another study suggested that the addition of RT to immune therapy could “allow for a prolonged response to immune checkpoint inhibition” (92).

Given the apparent low risk of combining immunotherapy with SRT, we have elected to expand the study population beyond those patients who have responded to and then progressed on immunotherapy, to include patients who have demonstrated disease control with immunotherapy but are no longer continuing to improve. In these cases, radiotherapy may provide improved disease control and symptom management. We will continue to explore the potential synergistic interactions of the immune-mediated abscopal effect with the anti-PD-1/PD-L1 activity of the allowed immunotherapy drugs.

2 OBJECTIVES

2.1 Primary Objective

To determine if SRT and PD-1/PD-L1 inhibiting therapy can restore the benefit of PD-1/PD-L1 inhibiting therapy in patients with an advanced solid tumor who had demonstrated disease control from PD-1/PD-L1 inhibiting therapy but did not continue to improve

2.2 Secondary Objectives

In patients who have received study treatment (SRT and PD-1/PD-L1 inhibitor):

2.2.1 To determine the response rate of SRT and PD-1/PD-L1 inhibiting therapy per unidimensional immune-related response criteria (irRC) and, if brain metastases are present, per iRANO

2.2.2 To determine the response rate at irradiated tumor sites

2.2.3 To determine the response rate at non-irradiated tumor sites

2.2.4 To determine the 2-year survival rate

2.2.5 To assess the toxicity associated with the study treatment

2.2.6 To assess the radiobiological and immunological characteristics of patients receiving study treatment using blood samples collected before and after SRT

2.3 Exploratory Objectives

2.3.1 To explore the use of volumetric measurements of tumor size for assessing response in patients who have received study treatment.

3 STUDY DESIGN

3.1 General Description

This study is a phase 2 single-arm clinical trial of SRT delivered concurrently with PD-1 or PD-L1 inhibiting therapy to determine if standard SRT potentiates the abscopal effect of PD-1 or PD-L1 inhibiting therapy in patients with an advanced solid tumor who previously achieved disease control from PD-1 or PD-L1 inhibiting therapy but are no longer continuing to improve. Eligible patients must have 1 to 5 metastatic, recurrent, or primary tumors that are clinically appropriate to receive SRT and at least one additional tumor that is measureable but will not be treated using SRT.

SRT will be delivered over 1 to 2 weeks. Patients will continue to receive the same FDA-approved PD-1 or PD-L1 inhibitor that they had been receiving previously until 52 weeks following completion of SRT.

Correlative blood samples will be collected at baseline, prior to the second SRT fraction, after the last SRT fraction (on the same day), and at 8, 24, and 52 weeks after the last SRT fraction. These samples will be used to determine the mechanistic immunologic effects of therapy.

3.2 Study Accrual

A Simon two-stage design will be employed to assess for treatment futility by examining treatment response in the first 11 patients at the 24-week post-SRT time point. If at least one patient has improved disease control, accrual will continue until a total of 41 patients have been enrolled in the study. Given the established safety profile of PD-1 pathway inhibition and SRT, an interruption in accrual after the first 11 patients have been accrued will not be required.

Refer to Section 1.6 and Section 13.2 for accrual restrictions for patients who receive SRT to brain metastases alone.

3.3 Primary Endpoint

Proportion of patients with improved disease control (see Section 13.1) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) and, if brain metastases are present, per Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) criteria at 24 weeks following SRT

3.4 Secondary Endpoints

3.4.1 Proportion of patients alive and free from progression (ie, CR, PR, or SD) per unidimensional irRC and, if brain metastases are present, per iRANO criteria at 24 weeks following SRT

3.4.2 Proportion of patients with treatment response (ie, CR, PR, or SD) at irradiated tumor sites at 24 weeks following SRT (refer to Section 10.1 for response criteria)

3.4.3 Proportion of patients with treatment response (ie, CR, PR, or SD) at non-irradiated tumor sites at 24 weeks following SRT (refer to Section 10.1 for response criteria)

3.4.4 Proportion of patients who are alive at 2 years after completion of SRT

3.4.5 Adverse events including the following:

- All SRT-related and immunotherapy-related ≥ grade 3 adverse events per the most current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0) occurring from initiation of SRT until 8 weeks after the last SRT fraction
- All immunotherapy-related adverse events (AEs) occurring from 8 weeks post-SRT until 2 years post-SRT requiring discontinuation of PD-1 or PD-L1 inhibiting therapy and concurrent initiation of immunosuppressive agents such as steroids as described in Section 8.5.2.

3.4.6 Radiobiological signature as described in Section 1.9.3 using blood samples collected prior to SRT (baseline), prior to the 2nd SRT fraction, immediately following completion of SRT (on same day); and at 8, 24, and 52 weeks following completion of SRT

4 PATIENT SELECTION

4.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for this study.

4.1.1 Pathologically-proven diagnosis of a solid tumor malignancy

4.1.2 One of the following criteria must be met:

4.1.2.1 Clinical or radiographic evidence of disease control (defined as best response of SD or PR or combination of both for ≥ 16 weeks) without evidence of CR or progression

OR

4.1.2.2 Clinical or radiographic evidence of disease progression during treatment with PD-1 or PD-L1 inhibiting therapy, following previous tumor response (CR, PR, or SD for ≥ 16 weeks) to PD-1 or PD-L1 inhibiting therapy,

and, for patients who discontinued PD-1 or PD-L1 inhibiting therapy during response to therapy, disease progression must have occurred following at least 8 weeks of re-treatment with PD-1 or PD-L1 inhibiting therapy

Note: Both the treating medical oncologist and radiation oncologist must be in agreement with determination of disease progression.

4.1.3 Administration of a PD-1 or PD-L1 inhibitor within 60 days prior to study registration

4.1.4 Determination by the treating radiation oncologist that the patient is a candidate for SRT (ie, radiation therapy with a stereotactic setup)

Note: All brain metastases will receive SRT.

4.1.5 The total number of tumors requiring SRT must be ≤ 5

Note: Regardless of the number of brain metastases that will be treated with SRT, the brain metastases will be considered to be one tumor.

4.1.6 Measurable disease by RECIST v1.1 that will not undergo SRT and that is amenable to monitoring

Note: As noted in Section 4.1.6, all brain metastases will receive SRT. Therefore, a patient with brain metastases that will be treated with SRT must also have extracranial disease that will not undergo SRT and that is amenable to monitoring (also see Section 1.6 and Section 13.2).

4.1.7 Determination by the treating medical oncologist that the patient is a candidate to continue the PD-1 or PD-L1 inhibiting therapy that had previously provided disease control

4.1.8 Age ≥ 18 years

4.1.9 Karnofsky Performance Status score of ≥ 60 % (see Appendix 1 for criteria)

4.1.10 A woman of childbearing potential (WCBP), defined as a woman who is < 60 years of age and has not had a hysterectomy, must have a documented negative serum pregnancy test within 14 days prior to initiating study treatment

4.1.11 Ability to understand and willingness to sign the consent form

4.2 Exclusion Criteria

4.2.1 Other anti-cancer therapy administered between the time of tumor response to PD-1 or PD-L1 therapy and time of study enrollment

Note: Patients treated with a combination of PD-1 or PD-L1 inhibiting therapy and other immunotherapy are eligible; patients taking hormonal anti-cancer therapies or steroids for central nervous system (CNS) edema management that, in the opinion of the investigator, are appropriate to continue are eligible.

4.2.2 Any prior PD-1/PD-L1 therapy-related AE that, in the opinion of the investigator, warrants exclusion from participation in this trial

4.2.3 Administration of any investigational agent within 4 weeks prior to initiating study treatment

4.2.4 Known active hepatitis B or C

4.2.5 Pregnancy or breastfeeding

4.2.6 Medical, psychological, or social condition that, in the opinion of the investigator, may increase the patient's risk or limit the patient's adherence with study requirements

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Study Entry Procedures

5.1.1 Required Pre-Registration Screening Tests and Procedures

Refer to the study calendar in Section 12 for the screening tests and procedures that are required prior to registration and for the timing of these events relative to the start of treatment.

5.1.2 Registration Process

Study registration will be performed by the study team [redacted]. The following documents are required for study registration:

- Completed, signed, and dated eligibility checklist
- Signed and dated consent form

The registrar will complete the registration process by assigning a study ID number. Study treatment may not begin until the Confirmation of Registration has been received and a study ID number has been assigned.

The study team submitting registration documents to the registrar will enter the patient's initial enrollment data (eg, demographics, consent, eligibility, on study) into the OnCore database within 24 hours following study registration (before the first SRT fraction).

5.2 Study Withdrawal

A patient may decide to withdraw from study participation at any time. Patients must be removed from the study when any of the following occurs:

- The patient has withdrawn consent for study treatment and study procedures
- If, in the investigator's opinion, continuation of the study requirements would be harmful to the patient's well-being
- The patient is lost to follow-up
- The sponsor has terminated the study

The reason for and date associated with study withdrawal or removal from the study must be documented in source documents and in the OnCore database.

6 STUDY TREATMENT

6.1 Baseline Tests and Procedures

Refer to the study calendar in Section 12 for requirements prior to initiation of study treatment. The tumor(s) anticipated to receive SRT (and at least one tumor that is measureable and will not be treated with SRT) and disease to be monitored should be identified using assessments completed prior to starting SRT.

6.2 Summary of Study Treatment

- Patients will receive a standard treatment regimen of SRT (refer to Section 6.3). The term SRT encompasses all radiotherapy using a stereotactic setup, both stereotactic radiosurgery (SRS) for metastatic lesions in the brain and stereotactic body radiotherapy (SBRT) for SRT delivered to all other locations. Registered patients will be designated as belonging to subgroups as follows:

  A. Patients receiving SBRT (body) irradiation only
  B. Patients receiving SBRT and SRS (body and brain) irradiation
  C. Patients receiving SRS (brain) irradiation only

- The same PD-1 or PD-L1 inhibitor that the patient was receiving prior to study registration will be continued after study registration. The PD-1 or PD-L1 inhibitor will be administered after the last SRT fraction (on the same day) and will continue to be given according to the schedule the patient was receiving prior to study registration through 52 weeks after the last SRT fraction. At the investigator's discretion, administration of the PD-1 or PD-L1 inhibitor may continue during Year 2 or longer (refer to Section 6.4 for additional scheduling information).

- At the treating medical oncologist's discretion, one dose of PD-1 or PD-L1 inhibitor may be given after study registration but prior to receiving SRT.

- All doses of the PD-1 or PD-L1 inhibitor administered after study registration will be given at the VCU Massey Cancer Center.

6.3 Stereotactic Radiotherapy

For the purposes of data collection and management, only the radiotherapy data required by the eCRFs for this trial will be captured in the database. The radiation treatment plan herein described is standard.

6.3.1 Radiation Oncology Department

All study patients will receive SRT in the MCC Radiation Oncology Department.

6.3.2 Dose Specifications

- Treatment will be planned to deliver a total of 18 to 60 Gy to the planning target volume (PTV) in up to 10 fractions over 1 to 2 weeks.
- The dose per fraction is to be prescribed so that at least 95% of the PTV receives the prescription dose.

  Note: Metastases in different locations may be treated to different doses in the same patient.

6.3.3 SRT Treatment Schedule

- SRT must begin **within 4 weeks** following study registration and be completed within 3 weeks after the first SRT fraction.

- The dates of computerized tomography (CT) simulation, start of RT, and completion of RT must be documented.
- The timing of treatment initiation should be coordinated with administration of the PD-1 or PD-L1 inhibitor, which must be given on the same day, after the last SRT fraction.

6.3.4 Treatment Planning

- Planning Constraints

  Planning constraints are provided in this section for both the PTV as well as critical normal structures to be spared. Acceptable treatment plans will be established from a DVH-based analysis of the volumetric dose to both the PTV and critical normal structures to ensure that minimally acceptable constraints for each volume of interest have been met.

- Planning Techniques

  Planning techniques may differ for each lesion to be treated provided that the tumor motion is properly accounted for with each technique when the target or targets are in or near the thorax region.

- Planning SRT Near Prior Radiotherapy Volumes

  The toxicity of delivering SRT to multiple metastases in close proximity to prior conventionally-fractionated external beam RT volumes is not known. Every effort should be made to limit the dose to organs at risk that have previously received radiation.

6.3.5 Technical Factors

- Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation, using a multileaf collimator or tomotherapy, is required.
- Daily image guidance is required. This can take the form of electronic portal imaging, orthogonal KV imaging, or cone beam CT.

6.3.6 Localization, Simulation, and Immobilization

- A custom immobilization device is suggested to minimize set-up uncertainty.
- CT-based simulation (maximum 3 mm slice thickness) is required.

6.3.7 Target Volumes and Contouring

- The gross tumor volume (GTV) is defined as all known gross disease as determined from a combination of clinical and radiographic examination.
- The internal target volume (ITV) is defined as all regions that are likely to harbor microscopic metastatic disease based on location and histology of the tumor and other involved sites as well as compensation for tumor motion.
- Normal structures should be contoured according to consensus guidelines such as Radiation Therapy Oncology Group contouring atlases, if available, or according to other commonly accepted contouring guidelines.

- The PTV will provide a margin around the ITV to compensate for the inter- and intra-fraction uncertainty consequent to daily set-up uncertainty and to potential internal organ motion. Depending on the site of the treated lesion and the immobilization technique used, the PTV will consist of a symmetrical 1-5 mm expansion around the ITV. In the event that PTVs extend outside of the skin surface, the clinician should manually trim the PTV contours to be 3-5 mm inside the outer skin (unless there is direct skin involvement).

6.3.8 Critical Structure Constraints

- Critical structure constraints will be specified according to the American Association of Physicists in Medicine Task Group (AAPM TG101) report (93). In the event that constraints for the number of fractions used are not listed in the report, dose constraints will be linearly interpolated from TG101 constraints.
- Use TG101 as a guide for dose limits to normal tissue. At a minimum, no organ at risk should receive greater than 105% of the prescription dose.
- In the event that a critical structure is encompassed in the PTV, the area of overlap will be limited to 105% of the prescription dose.

6.3.9 Metastasis Location Definition for Treatment Planning

Each metastasis targeted with SRT will be assigned to one of the 8 “Metastasis Locations” as described in this section.

6.3.9.1 Lung Central

- GTV within 2 cm of proximal bronchial tree: Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi)
- Tumors that are immediately adjacent to mediastinal or pericardial pleura (ie, PTV touching the pleura) also are considered central tumors

6.3.9.2 Lung Peripheral

Metastases within the lung parenchyma with GTV outside of the proximal bronchial tree as described above

6.3.9.3 Mediastinal/Cervical Lymph Nodes

- Mediastinal

  GTV arising within the anatomic space between the lungs, above the diaphragm, and below the thoracic inlet at the level of the top of the sternal notch

- Cervical lymph nodes

  GTV occurring within cervical lymph node Levels I-VI and/or retropharyngeal spaces; superior border skull base

- Sternal metastases

Assigned to the mediastinal/cervical lymph node location based on potential for normal tissue toxicity

6.3.9.4 Liver

- GTV arising within the liver
- Rib metastases immediately adjacent to the liver assigned to the liver metastasis location

6.3.9.5 Spinal

- Metastases assigned to the spinal/paraspinal site if the GTV arises within the vertebral bodies expanded by 1 cm. Spinal metastases can involve the vertebral body only **or** the vertebral body and pedicle **or** posterior elements only.

  For each of these metastases, the PTV delineation will include:

  - Involved vertebral body and both pedicles **or**
  - More generous delineation of the involved vertebral body and both pedicles **or**
  - Involved vertebral body, both pedicles, and the anterior and posterior elements of the spine **or**
  - Spinous process and laminae

  The target volume may be chosen at the discretion of the treating radiation oncologist based on the extent of tumor involvement.
- Spinal metastases with epidural extension will only be included if there is > 3 mm gap between the edge of the epidural metastasis and edge of the spinal cord.
- Metastases arising in the ribs within 1 cm of the edge of the vertebral body should be included in the spinal metastasis location, but osseous metastases planning guidelines are to be used.

6.3.9.6 Osseous

- GTV arising within an osseous structure, part of the axial skeleton, not included in the spinal definition.
- Rib metastases that are within 1 cm of the vertebral bodies are to be classified into the spinal metastasis location given the similar normal tissues at risk.
- Rib/scapular metastases within the thorax adjacent to lung parenchyma are to be classified into the lung metastasis location given the similar normal tissues at risk.
- Rib/osseous metastases adjacent to mediastinal or cervical structures are to be classified into the mediastinal/cervical lymph node location given the similar normal tissues at risk.

- Rib metastases adjacent to the liver are to be classified into the liver location given the similar normal tissues at risk.
- Rib metastases adjacent to the stomach/abdominal wall are to be classified into the intra-abdominal location given the similar normal tissues at risk.
- Sternal metastases are to be considered part of the mediastinal/cervical lymph nodes location given the similar normal tissues at risk.
- Metastases arising in the bones of the skull are to be included in the brain metastasis location but osseous metastases planning guidelines are to be used.

6.3.9.7 Abdominal-pelvic

GTV arising within the anatomic space defined by the diaphragm superiorly, the genitourinary diaphragm inferiorly including the peritoneal and retroperitoneal spaces, not including the liver, osseous, or spinal metastases

6.3.9.8 Brain

- GTV arising within the anatomic space defined by skull base inferiorly, within 1 cm of brain parenchyma, and not including osseous metastases
- If above skull base but not within 1 cm of brain parenchyma, then include as osseous metastasis

6.3.10 Labeling Target Structures

Target structures will be labeled as gross tumor volume (GTV), internal target volume (ITV) if applicable, and planning target volume (PTV). The prescription dose in cGy will follow the structure names separated by an underscore. Each should be labeled according to numerical order of the anatomical sites described in Section 6.3.9 (eg, PTV_5000_2 is a peripheral lung lesion receiving 50 Gy while PTV_5000_4 is a liver lesion receiving 50 Gy). If multiple lesions exist within a single anatomical site, each lesion can be distinguished by adding a letter to the end of the PTV name (eg, PTV_5000_1a and PTV_5000_1b). Brain lesions can also include an anatomic descriptor (eg, PTV_2700_8a_ left parietal).

6.3.11 Supportive Care

Supportive care for management of symptoms related to SRT is at the discretion of the radiation oncologist.

6.4 Administration of the PD-1 or PD-L1 Inhibiting Therapy

The following instructions regarding the administration of the PD-1 or PD-L1 inhibitor will be followed:

6.4.1 PD-1 or PD-L1 Inhibitor

The patient must continue to receive the same PD-1 or PD-L1 inhibitor that had been administered prior to study registration.

6.4.2 Preparation and Administration of the PD-1 or PD-L1 Inhibitor

Refer to the current agent-specific prescribing information for instructions regarding preparation and administration of the PD-1 or PD-L1 inhibitor.

6.4.3 PD-1 or PD-L1 Inhibitor Treatment Schedule

- The timing of the pre-SRT dose of the PD-1 or PD-L1 inhibitor (if given) must be planned to allow the second PD-1 or PD-L1 inhibitor dose to be administered on the last day of SRT (following the last SRT fraction).

  Note: Administration of an on-study PD-1 or PD-L1 inhibitor prior to initiation of the SRT is not required, but one pre-SRT dose is permitted. (See Section 4.1.4 regarding requirements prior to study registration.)

- The PD-1 or PD-L1 inhibitor will continue to be administered according to the prescribing information for the agent the patient is receiving. At the discretion of the treating medical oncologist, modifications in treatment schedule are permitted.

6.4.4 Duration of PD-1 or PD-L1 Inhibiting Therapy

The PD-1 or PD-L1 inhibitor will continue until 12 months following completion of SRT. At the treating investigator's discretion, the PD-1 or PD-L1 inhibitor may be continued during Year 2 (or longer) if the patient continues to tolerate treatment and is receiving clinical benefit.

6.4.5 Assessment and Management of PD-1 or PD-L1 Inhibiting Therapy Side Effects

Information and instructions found in the applicable prescribing information should be followed. However, management of side effects is at the discretion of the treating medical oncologist.

6.4.6 Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating medical oncologist. Supportive care measures for the management of AEs with potential immunologic etiology are provided in the prescribing information for the specific PD-1 or PD-L1 inhibitor.

6.5 Prohibited Medications and Treatments

6.5.1 Cancer Treatment

Once study therapy is initiated, cancer treatment (eg, chemotherapy, biological therapy, immunotherapy, RT) other than the treatment specified in the protocol for this study is not permitted until disease progression. Continuation of hormonal anti-cancer therapy is permitted at investigator discretion. Steroids for CNS edema management are considered supportive care, not anti-cancer treatment.

6.5.2 Other Medications

- Live vaccines (examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine) are prohibited.
- Administration of investigational agents is not permitted until disease progression (see Section 5.2 regarding study withdrawal).

6.5.3 Concurrent Medications

Concurrent medications will be recorded in source documents at visits in accordance with the study calendar. The only concurrent medications required to be captured in eCRFs are:

- Oral or parenteral steroids
- Any immunotherapy given other than PD-1 or PD-L1 inhibitor (see Section 4.2.1)
- Any hormonal therapy being used for cancer control (see Section 4.2.1)
- Any prohibited medication (see Sections 6.5.1 and 6.5.2)

6.6 Duration of Therapy

Study treatment will be administered as described in Sections 6.3 and 6.4 unless one of the following occurs (also see study withdrawal criteria in Section 5.2):

- AE that requires discontinuation of study treatment
- Pregnancy
- Determination by the investigator that discontinuation is in the patient's best medical interest
- Patient decision to discontinue study treatment
- Withdrawal of study sponsor support

The reason for discontinuation of study treatment must be documented in the source documents and in the OnCore database.

6.7 Follow-Up Period

6.7.1 For AE Evaluation and Reporting

6.7.1.1 AEs Related to SRT and/or PD-1 or PD-L1 Inhibiting Therapy

Assessment and reporting for all ≥ grade 3 AEs will continue through 8 weeks following the last SRT fraction (Section 8.5.1).

6.7.1.2 AEs Related to PD-1 or PD-L1 Inhibiting Therapy

Assessment and reporting of selected AEs related to the PD-1 or PD-L1 inhibiting therapy as described in Section 8.5.2 will continue until the PD-1 or

PD-L1 inhibitor has been discontinued (for any reason) or until 2 years after completion of SRT, whichever occurs first.

6.7.2 Follow-up for Treatment Response and Survival

Patients who remain on study will be assessed according to the study calendar (Table 5) through 2 years after completion of SRT.

7 DOSING DELAYS/DOSING MODIFICATIONS

7.1 SRT

There are no study-specified requirements for modification in the SRT treatment plan. However, the treating radiation oncologist may modify the fraction dose and/or schedule if necessary for patient safety.

7.2 PD-1 or PD-L1 Inhibitor

Dose reductions and/or treatment delays due to immune-related side effects of the PD-1 or PD-L1 inhibitor will be permitted at the discretion of the treating medical oncologist. The instructions for dosing delays and/or modifications provided in the prescribing information for the specific PD-1 or PD-L1 inhibitor can be referred to in making treatment modification decisions.

8 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

8.1.2 Serious AE (SAE)

An AE is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening AE,

  An AE is considered to be “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization,

  Planned inpatient hospitalizations, eg, for planned surgery, or those that occur for logistical reasons, eg, to complete a therapy that cannot be completed due to outpatient clinic business hours, are exempt from SAE reporting. Events that

prolong such hospitalizations and otherwise meet reporting criteria are, however, still subject to SAE reporting requirements.

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Unanticipated Problem

An unanticipated problem (UP) includes any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the institutional review board (IRB); and (b) the characteristics of the patient population being studied;
- 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 patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.4 AE Description and Grade

The descriptions and grading scales found in the revised CTCAE v5.0 will be utilized for AE reporting.

8.1.5 AE Expectedness

AEs can be ‘Unexpected’ or ‘Expected’.

- Expected AEs are those AEs, the specificity and severity of which, are listed or described in the current version of the FDA-approved prescribing information for the specific PD-1 or PD-2 inhibitor.
- Unexpected AEs are those AEs occurring in one or more patients participating in the study, the nature, severity, or frequency of which is not consistent with either:
  - The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related document, such as the IRB-approved research protocol and the current IRB-approved informed consent document, and (b) the FDA-approved prescribing information.
  - The expected natural progression of any underlying disease, disorder, or condition of the patient(s) experiencing the AE and the patient’s predisposing risk factor profile for the AE.

8.1.6 AE Attribution

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

8.2 Known AEs Associated with Stereotactic Radiotherapy

Fatigue is likely to occur for all treatment locations with an expected duration of < 8 weeks. Other AEs related to SRT for the treatment of metastases depend on the location of the lesions treated and exposure of surrounding normal tissues. The following list contains examples of possible SRT-related AEs but is not all-inclusive, given the diversity of sites that may be irradiated in this trial.

8.2.1 Lung (Central and Peripheral), Mediastinal/Cervical Lymph Node Metastases

- Cardiac and pericardial injury

  Cardiac and pericardial injury is uncommon in the conventionally-fractionated course of RT, side effects can be seen with large doses per fraction of SRT.

- Gastrointestinal/Esophageal injury

  Esophagitis (ie, dysphagia causing pain on swallowing) relatively soon after SRT is completed; typically resolves on its own within days to a week or longer

- Central Airway/Bronchial injury

  Bronchial toxicity includes:

  - Cough
  - Dyspnea
  - Hypoxia
  - Pleural effusion
  - Pleuritic pain associated with collapse
  - Bronchial necrosis/fistula
  - Hemoptysis/pulmonary hemorrhage

- Lung injury

  Radiation pneumonitis (ie, inflammation of the end bronchioles and alveoli); toxicities include:

  - Fever
  - Shortness of breath
  - Pulmonary infiltrate on chest x-ray

8.2.2 Liver/Abdominal-Pelvic Metastases

- Skin irritation, redness, itchiness, discomfort
- Asymptomatic decrease in blood counts
- Asymptomatic increase in liver enzymes
- Nausea and vomiting
- Gastric, esophageal, small bowel or large bowel irritation, ulceration, and/or bleeding
- Fistula
- Obstruction or changes in motility following therapy
- Chest wall pain
- Radiation-induced liver disease (RILD)
  - Classic RILD: Anicteric ascites, hepatomegaly, and elevation of alkaline phosphatase relative to other transaminases that may occur following SRT to the liver
  - Non-classic RILD: Elevation of liver enzymes and/or any decline in liver function
- Liver failure
- Permanent thrombocytopenia
- Bleeding

8.2.3 Spinal Metastases

- Radiation myelitis
- Radiation esophagitis
- Radiation laryngitis or pharyngitis
- Radiation pneumonitis

8.2.4 Osseous

- Erythema
- Desquamation
- Pain
- Edema
- Neuralgia

8.2.5 Brain

- Nausea/vomiting
- Seizure
- Headache

8.3 Known AEs Associated with PD-1 or PD-L1 Inhibiting Therapy

Refer to the current prescribing information for the known AEs associated with the PD-1 or PD-L1 inhibitor the patient is receiving.

8.4 Secondary Malignancy

A secondary malignancy is a new cancer caused by previous treatment for a malignancy, eg, chemotherapy or RT. Metastatic disease is not a secondary malignancy. Any secondary malignancy should be reported via expedited reporting mechanisms.

8.5 Time Period and Grade of AE Capture

8.5.1 From Initiation of SRT Until 8 Weeks Post-SRT

All SRT-related and immunotherapy-related **≥ grade 3** AEs will be recorded beginning at the time of the first SRT fraction and continuing until 8 weeks following completion of SRT.

8.5.2 After 8 Weeks Post-SRT

Only AEs requiring that the PD-1 or PD-L1 inhibitor be discontinued **and** that steroids be administered will be recorded beginning after the 8-week post-SRT AE assessment.

8.6 Procedures for Recording AEs, SAEs, and UPs

All AEs, SAEs, and UPs will be recorded in MCC's OnCore Clinical Trials Management System. In most cases, it is acceptable to record in OnCore only the highest grade of a toxicity occurring during a particular study segment when an event has serial fluctuations in grade over time.

SAE's will be entered into the OnCore SAE domain. UPs will be entered into the OnCore Deviations domain. An SAE that is both an SAE and a UP will be entered in both domains. For all SAEs, a corresponding entry should be made in the routine AE record to match the event entries in the SAE domain.

8.7 Expedited Reporting Procedures

Refer to Table 1 for expedited reporting requirements and instructions.

Table 1. Expedited Reporting Requirements

SAEs[A]	UPs[B]
Principal Investigator[C] Alfredo Urdaneta, MD [redacted]	**Principal Investigator**[C] Alfredo Urdaneta, MD [redacted]
Study Team[C] Daeryl Williamson, RN, BSN [redacted]	**Study Team**[C] Daeryl Williamson, RN, BSN [redacted]
	DSMC[D] [redacted]
	IRB[E]

A. Refer to Section 8.1.2 for SAE definition. After the 8-week post-SRT assessment, only AEs meeting the criteria outlined in Section 8.5.2 will be recorded; if the AE is an SAE, the event will be reported in an expedited manner as noted on this table.

B. Refer to Section 8.1.3.

C. Report event within 1 business day of becoming aware of the occurrence.

D. Report event within 2 business days of becoming aware of the occurrence.

E. Report each UP to the VCU IRB within 5 business days of becoming aware of the occurrence.

9 PHARMACEUTICAL INFORMATION

[redacted]

10 MEASUREMENT OF EFFECT

10.1 Criteria for Tumor Response

Objective criteria will be used to assess tumor response in this study. RECIST v1.1 and unidimensional irRC will be used at each assessment time point. RANO-BM and iRANO criteria will be used to determine tumor response in the brain, if the brain metastases were treated with SRT. The criteria to be used for tumor response-related endpoint analyses are as follows:

- RECIST v1.1 (94)
- RANO-BM Criteria for patients with brain metastasis (95)
- Unidimensional irRC (96) modified to permit use of short-axis measurement for lymph nodes, in line with RECIST v1.1; also refer to Table 2
- iRANO criteria for patients with brain metastasis (97); also refer to Table 3

Table 2. Unidimensional Immune-Related Response Criteria

Guidelines	
New, measurable (ie, ≥ 10 mm) lesions	Incorporated into tumor burden [A]
New, nonmeasurable lesions	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
Response	**Criteria**
Complete Response (irCR)	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
Partial Response (irPR)	≥ 30% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart
Stable Disease (irSD)	Does not meet criteria for irCR, irPR, or irPD
Progressive Disease (irPD)	At least 20% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart
A. Tumor Burden = the sum of unidimensional diameters of targets and new lesions	

Table 3. RANO-BM and iRANO Criteria for Brain Metastasis

Response	RANO-BM Criteria*
Complete Response	Disappearance of all CNS target lesions for ≥ 4 weeks; disappearance of all enhancing CNS non-target lesions; no new lesions; no steroids; clinically stable or improved
Partial Response	≥ 30% decrease in sum of longest diameters of target lesions for ≥ 4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved
Stable Disease	Does not qualify for complete response, partial response, or progressive disease
Progressive Disease	≥ 20% increase in the sum of longest diameters of target lesions; and at least one lesion must increase by an absolute value of 5 mm or more; or unequivocal progression of existing enhancing non-target CNS lesions; or new lesions; or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions
*iRANO recommends confirmation of disease progression on follow-up imaging 3 months after initial radiographic progression if there are no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medications and if the patient's duration on the current immunotherapy regimen is 6 months or less. For this trial, that 6-month window will begin with the initiation of protocol therapy and not that patient's first exposure to immunotherapy. If follow-up imaging confirms disease progression, the date of actual progression should be back-dated to the date of initial radiographic progression. The appearance of new lesions 6 months or less from the initiation of protocol therapy alone does not define progressive disease.	

10.2 Tumor Response Requirements

10.2.1 Time Points for Assessment of Tumor Response

Objective disease assessment will be performed at the following time points:

- At baseline (before SRT begins)
- At 8 weeks (+/- 2 weeks) after the last SRT fraction
- At 16 weeks (+/- 2 week) after the last SRT fraction
- At 24 weeks (+/- 2 week) after the last SRT fraction
- If needed, at approximately 28 weeks (at least 4 weeks after the 24-week tumor response assessment), an additional objective disease assessment may be performed to confirm response status

At the investigator's discretion, additional assessments may be performed when clinically indicated.

10.2.2 Imaging

Only imaging of the initial sites of disease is required at subsequent time points to provide tumor measurements for assessment of antitumor effect. The same type of imaging used at baseline should be used at each scheduled assessment.

10.2.3 Clinical Examination

- Per RECIST v1.1 and unidimensional irRC, imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but can be assessed by clinical exam.
- Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (eg, skin nodules).

10.3 Central Review for Imaging Interpretation

Central radiologic review for evaluation of tumor response will only be conducted for patients who have CR, PR, or SD by internal review at the **24-week** disease assessment time point.

11 CORRELATIVE STUDIES

Refer to Section 1.8 for a description of the plans for correlative studies using collected blood samples.

11.1 Patient Participation

Participation in the correlative studies using blood samples is a study requirement for all patients.

11.2 Collection, Processing, and Distribution of Samples

- The study team will coordinate collection and de-identification of all correlative blood samples.
- Questions regarding study requirements should be directed to the study team. The Principal Investigator should be contacted in the event that a correlative sample must be missed or is found to be inadequate.

11.3 Blood Sample Collection Time Points

Blood samples will be collected at the following 6 time points:

- Prior to initiation of SRT (after study registration)
- Prior to the 2nd SRT fraction
- After the last SRT fraction (**on the same day**)
- At the following time points after the last SRT fraction:
  - At 8 weeks (+/- 2 weeks)
  - At 24 weeks (+/- 2 weeks)

- At 52 weeks (+/- 4 weeks)

11.4 Instructions for Blood Sample Collection

At each time point:

- Collect 10 mL of blood in a purple-top tube
- Invert 8-10 times after collection and deliver at ambient temperature within 2 hours following collection to the laboratory of Ross Mikkelsen, PhD in the Department of Radiation Oncology.

11.5 Blood Sample Labeling

Each collected blood sample should be labeled as follows:

- Study number
- Patient study identification number
- Date of sample collection
- Time of sample collection
- Study time point

11.6 Testing and Analysis

Testing and analysis of the blood samples will be performed by Dr. Ross Mikkelsen and Dr. Xiang-Yang (Shawn) Wang.

11.7 Tracking Blood Samples

Collection and distribution of all blood samples will be logged by the study team in OnCore.

12 STUDY CALENDARS

Required tests, exams, collection of samples for correlative studies, and study treatment are listed on 2 tables: requirements during screening on Table 4 and requirements during treatment and follow-up on Table 5. At the discretion of the treating radiation oncologist, additional SRT-related standard tests and exams may be performed. At the discretion of the treating medical oncologist, additional tests may be performed to continue the standard care the patient was receiving during PD-1 or PD-L1 inhibiting therapy prior to study registration.

Table 4. Study Calendar – Screening Requirements

Tests, Exams, and Other Requirements	Prior to Study Registration
Informed Consent	Prior to study-specific procedures
Medical/Surgical History [A]	Within 28 days
Demographics	
Tumor Imaging [B]	
Disease Assessment [C]	
Radiation Oncology Consultation [D]	
Medical Oncology Consultation [E]	
Concurrent Medications [F]	Within 14 days
Baseline Conditions and Symptoms	
Baseline Assessment of prior and ongoing PD-1/PD-L1-related AEs [G]	
Physical Exam	
Height and Weight	
Vital Signs including BP	
Performance Status (Appendix 1)	
CBC with Differential; Platelets	
Serum Chemistry [H]	
Pregnancy Test [I]	

A. Assessment of Medical History will include, if known, baseline tumor characteristics: PD-L1 expression and Microsatellite Instability-High (MSI-H) status

B. Baseline imaging **should be contrast-enhanced** and include the following:

- CT, PET-CT, and/or MRI of all suspected sites of disease within 28 days prior to study registration; for patients with a documented CT and/or MRI contrast allergy, the CT and/or MRI may be performed without contrast.
- Brain (CT or MRI) **within 1 year** prior to study registration to screen for brain metastasis. In patients with known brain metastasis, brain imaging must be performed within 28 days prior to study registration.

Note: The imaging used at baseline should be used at each subsequent imaging time point.

C. Disease assessment by imaging and/or clinical examination. For patients with brain metastasis receiving SRS, disease assessment includes documentation of neurologic status and dosing history of steroids used for CNS edema management.

D. To determine if the patient is a candidate for SRT and if there is at least one lesion that will not receive SRT.

E. Consultation or, if the patient's treating medical oncologist is a VCU MCC sub-investigator, documentation that the patient is a candidate to continue PD-1 or PD-L1 inhibiting therapy.

F. Refer to Section 6.5.3.

G. Assessment to determine if AEs related to previous therapy have resolved or stabilized.

H. Chemistry includes the following panels and tests: basic metabolic panel (sodium, potassium, carbonate, chloride, glucose, calcium, BUN, and creatinine); hepatic panel (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, and total protein).

I. Only required for WCBP (see Section 4.1.12); if required, perform within 14 days prior to study registration. If SRT cannot begin within 14 days of a negative pregnancy test, the pregnancy test must be repeated prior to initiation of SRT. Serum or urine qualitative pregnancy test is acceptable.

Table 5. Study Calendar – On-Study, Study Treatment, and Follow-Up

Requirements	On Study	During SRT		Follow-Up Post-SRT in Year 1 (Weeks)					Follow-Up in Year 2
		Week 1	Week 2	4 [A]	8 [B]	16 [B]	24 [B]	52 [C]	
Weight				X	X		X		
Performance Status (Appendix 1)				X	X		X		
Assessment of AEs (Section 8)		X		X	X	X [D]	X [D]	X [D]	X [E]
Concurrent Medications [F]				X			X		
Physical Exam				X	X		X		
CBC with Differential				X	Frequency per Treating Investigator [H]				
Serum Chemistry [G]				X					
Pregnancy Test	X [I] (if required)								
Imaging/Disease Assessment [J]					X [K]	X	X [L]	X [M]	X [N]
Collection of Correlative Blood Samples (Section 11)	X (prior to 1st SRT fraction)	X (prior to 2nd SRT fraction)	X (after last SRT fraction on same day)		X		X	X [O]	
SRT (Section 6.3)		X (up to 10 fractions over 1-2 weeks) [P]							
Administration of PD-1 or PD-L1 Inhibitor (Sections 6.2 and 6.4)	X (prior to 1st SRT) [Q]	X (after last SRT fraction on same day)		X Continue According to Prescribing Information Until 12 Months Following Last SRT Fraction					X [R]
Survival Follow-Up									X [S]

Table 5 Footnotes:

A. Within +/- 1 week.

B. Within +/- 2 weeks.

C. Within +/- 4 weeks.

D. Assessment and reporting limited to AEs that required discontinuation of the PD-1/PD-L1 inhibitor **and** steroid management.

E. AEs will continue to be assessed every 2-6 months through end of year 2 in those who continue on PD-1 or PD-L1 inhibitor therapy in accordance with Section 6.7.

F. Refer to Section 6.5.3.

G. Serum chemistry includes the following panels and tests: basic metabolic panel (sodium, potassium, carbonate, chloride, glucose, calcium, BUN, and creatinine); hepatic panel (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, and total protein).

H. After week 4, labs are done as part of routine care assessments, and these lab values are not required to be entered in eCRFs. They will be reviewed as part of AE assessments and, as applicable, AE eCRF entry.

I. For WCBP, the pregnancy test must be repeated if the pre-entry test was performed more than 14 days prior to initiation of SRT. If required, either a urine or serum qualitative pregnancy test may be performed.

J. The imaging (and/or clinical assessment) used at baseline should be used at each subsequent time point; refer to Section 10.1 for information regarding the response criteria to be used. For patients with brain metastasis receiving SRS, disease assessment includes documentation of neurologic status and dosing history of steroids used for CNS edema management.

K. A goal of imaging at 8 weeks post-SRT is to rule out progressive disease.

L. Imaging findings at the 24-week time point will be used for analysis of the primary endpoint (Section 13.3). Refer to Section 10.3 regarding central review requirements. An optional disease assessment may be done at approximately 28 weeks (at least 4 weeks after the 24-week disease assessment) if needed to confirm response status.

M. In the absence of post-SRT disease progression, continue with imaging and disease assessment every 2-3 months until 12 months following completion of SRT.

N. In the absence of post-SRT disease progression, continue with imaging every 2-6 months until 2 years following completion of SRT. (If the patient has initiated a new cancer treatment, imaging is no longer required.)

O. If the patient is available and willing to have a final blood sample collected for the correlative studies.

P. SRT must be administered by VCU Radiation Oncology and must begin within 4 weeks following study registration; refer to Section 6.3 for additional SRT requirements and instructions.

Q. If one dose of the PD-1 or PD-L1 inhibitor needs to be given after study registration (before the first SRT fraction), the pre-SRT dose (if given) must be timed so that the next dose is given on the same day as the last SRT fraction.

R. At the discretion of the treating medical oncologist, the PD-1 or PD-L1 inhibitor may continue to be administered after 52 weeks following completion of SRT if there has not been disease progression following SRT.

S. For patients with post-SRT disease progression, follow-up can be limited to assessment of vital status until 2 years after completion of SRT.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a single-arm phase 2 study of SRT and PD-1 or PD-L1 inhibiting therapy for patients with advanced solid tumors who achieved disease control during PD-1 or PD-L1 inhibiting therapy. The primary objective is to determine if SRT can restore the benefit of PD-1 or PD-L1 inhibiting therapy in patients with an advanced solid tumor who had disease control from PD-1 or PD-L1 inhibiting therapy but did not continue to improve. For patients enrolled with progression, this would mean SD, PR, or CR. For patients enrolled with stable or plateaued disease, restoration of benefit would be an objective response, ie PR or CR.

13.2 Sample Size and Accrual Rate

Given that only approximately 10% of patients who continue PD-1 or PD-L1 inhibition after progression or plateau on a prior PD-1 or PD-L1 inhibiting agent experience improved disease control (18, 45, 98), we would consider an improved disease control rate of 25% (relative to 10% of patients who do not receive radiotherapy) with the combination of SRT and PD-1 or PD-L1 inhibiting therapy to be promising and worthy of further study. To statistically test whether the disease control improvement rate meets our disease control criteria, the study will require a sample size of 42 evaluable patients to have 80% power at 5% level of significance. We anticipate that 10% of enrolled patients may be inevaluable; therefore, up to 46 patients are required to ensure that sufficient patients will be evaluable. Patients who are not evaluable for efficacy as defined in Section 13.5.2 will be replaced.

Given the limited data on the immunogenicity of brain metastases, enrollment of patients who receive SRT to brain metastases alone will be limited to no more than 4 of the first 14 evaluable patients and no more than 11 of the 37 evaluable patients. Patients who receive SRT to other sites as well as to brain metastases will not be counted towards this allotment.

Accrual is anticipated to be about 1 patient every 1-2 months over a period of about 4.5 years.

13.3 Statistical Analysis of Primary Objective

We will employ a Simon two-stage design to assess for treatment futility by examining the rate of improved disease control at 24 weeks following completion of SRT. Therefore, 14 patients will be evaluated for the primary endpoint (ie, improved disease control) at 24 weeks. If at least 2 successes are observed, we will continue to recruit a total of 42 evaluable patients. If fewer than 2 successes are observed, then the study will close to further accrual. If 8 or more success are observed in the total population of 42 evaluable patients, further investigation of this treatment regimen will be considered warranted.

At the end of the first stage, all primary and secondary endpoints will be summarized and shared with the Data Safety and Monitoring Committee (DSMC). If the study goes into the second stage of accrual, this will be the interim analysis. If early termination of the study is recommended, this will be the final analysis.

The rate of improved disease control will be reported with a point estimate and 95% confidence interval. Analysis of the primary objective will include all efficacy-evaluable patients; however, a subset analysis of efficacy-evaluable patients who only receive SRT to brain metastases will also be performed.

13.4 Statistical Analysis of Secondary Objectives

Patients' demographics, AEs and SAEs, disease status, treatment status, clinical response, etc will be listed and summary descriptive statistics will be calculated. Rate of higher grade AEs will be reported at each follow-up visit.

Time to death, time to progression at the irradiated site, and time to progression at a non-irradiated site will be summarized using the Kaplan Meier survival curve. Overall survival probabilities will be estimated with 95% confidence intervals at each follow-up time point during the 2-year follow-up. Analysis of the secondary objectives will include all evaluable patients; however, a subset analysis of evaluable patients who only receive SRT to brain metastases will also be performed.

13.5 Analysis Populations

13.5.1 Safety-Evaluable Population

Patients who have received at least 1 SRT fraction and at least one dose of PD-1 or PD-L1 inhibiting therapy after SRT will be evaluable for safety and toxicity analyses.

13.5.2 Efficacy-Evaluable Population

Patients will be evaluable for analysis of the primary endpoint if they meet all of the following criteria:

- Received at least 50% of the prescribed SRT
- Received at least one dose of PD-1 or PD-L1 inhibiting therapy after SRT
- Had baseline and at least one subsequent response assessment to measure the SRT-treated tumor **and** the non-SRT-treated tumor following the last dose of SRT as follows:
    - Patients with documented unequivocal progression of disease prior to the 24-week time point will be evaluable.
    - Patients who do **not** have documented unequivocal progression of disease prior to the 24-week time point **and have not** had an objective response assessment at the 24-week time point will not be evaluable for efficacy and will be replaced.

14 DATA AND SAFETY MONITORING

14.1 Study Team

The study team minimally consists of the Principal Investigator, the research nurse, the clinical research associate, and the study biostatistician. While patients are on treatment,

the Principal Investigator, the research nurse, and the clinical research associate will meet at least monthly to review study status; quarterly meetings will be held with the study biostatistician. This review will include, but not be limited to, reportable SAEs and UPs and an update of the ongoing study summary that describes study progress. All meetings, including attendance, are documented.

14.2 Monitoring and Auditing

14.2.1 MCC Compliance Office

Compliance specialists in the MCC Compliance Office will provide ongoing monitoring and auditing for this study.

14.2.2 Data Safety and Monitoring Committee

The study will be reviewed by the MCC DSMC initially according to the risk level specified by the MCC Protocol Review and Monitoring Committee (PRMC) and then according to a schedule based on study status and quality indicators. The DSMC will review reports provided by the Principal Investigator/study team and the MCC Compliance Office focusing on data integrity and patient safety.

15 REGULATORY COMPLIANCE AND ETHICS

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Patients of Research* (US National Commission for the Protection of Human Patients of Biomedical and Behavioral Research, April 18, 1979).

15.2 Regulatory Compliance

This study will be conducted in compliance with the clinical trial protocol and with federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Patients/Informed Consent); 21 CFR 56 (Institutional Review Boards); 21 CFR 312 (IND Application); and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children).

15.3 Institutional Review Board

The VCU IRB, which is registered with the Office for Human Research Protections (OHRP), must review and approve the protocol, the associated informed consent document, and recruitment material (if any). Any amendments to the protocol or consent form must also be approved.

15.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion of risks and possible benefits of this therapy will be provided to patients and

their families. Consent forms describing the study interventions/study procedures and risks are given to the patient and written documentation of informed consent is required prior to starting intervention/administering study product. Presentation, discussion, and completion of the consent form will occur at the MCC.

Consent forms will be IRB-approved and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to patients for their records; the original consent form will be maintained in the research records. The rights and welfare of patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.5 Patient Confidentiality

Patient confidentiality is strictly held in trust by the Principal Investigator, participating investigators, staff, and the sponsor and its agents. This confidentiality includes the clinical information relating to participating patients, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

The Principal Investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections. Source documents provided for the purpose of auditing or monitoring will be de-identified and labeled with the study number, patient ID number, and patient initials.

The study monitor or other authorized representatives of the Principal Investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

16 DATA COLLECTION AND MANAGEMENT

16.1 Data Management Responsibilities

The Principal Investigator is responsible for: (i) reviewing SAE reports; and if so, filing the report;

The Principal Investigator is responsible for: (i) the overall conduct of the investigation; (ii) ongoing review of trial data including all safety reports; and (iii) apprising participating investigators of any UPs.

The Principal Investigator is responsible for: (i) the data management; and (ii) reporting SAEs, UPs, and other events requiring expedited reporting as described in Section 8.7.

Any laboratory conducting correlative studies must maintain the laboratory records and documentation (laboratory notebooks, laboratory protocols, print-outs, recordings, photographs, etc.)

16.2 CRFs and Data Collection

MCC OnCore data management will provide standard electronic CRFs (eCRFs) and create study-specific eCRFs to be able to capture all information required by the protocol. The eCRFs will be approved by the study team to ensure the most effective data acquisition.

The investigator(s) and study coordinator(s) must maintain source documents for each patient in the study. All information on eCRFs will be traceable to these source documents, which are generally maintained in the patient's file.

All eCRFs should be completed and available for collection within a timely manner, preferably no more than 14 days after the patient's visit.

16.1 OnCore Data Entry

Data will be entered into MCC's OnCore database on an ongoing basis by the study team. The study team is responsible for updating data to allow for data compilation and review. The electronic data submissions will be reviewed periodically for data timeliness and accuracy.

16.2 Study Record Retention

As applicable, study records will be maintained a minimum of 6 years beyond the publication of any abstract or manuscript reporting the results of the protocol or submission of a final report to clinicaltrials.gov.

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APPENDIX 1. PERFORMANCE STATUS CRITERIA

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