UMCC 2017.069

FAST: **F**easibility trial of **A**nti-PD(L)1 and **S**BRT in the **T**reatment of Advanced, Platinum-Refractory Urothelial Carcinoma

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Study Drug: Pembrolizumab (Keytruda ®)

Initial version: August 18, 2017
Amendment: December 19, 2017
February 14, 2018
October 5, 2020

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
Anti-PD(L)1	Anti-Programmed Death (Ligand) 1
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
p.o.	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
UaP	Unanticipated Problem
UMCCC	University of Michigan Comprehensive Cancer Center
WBC	White Blood Cells

STUDY SCHEMA

SBRT and Anti-PD(L)1 Schedule

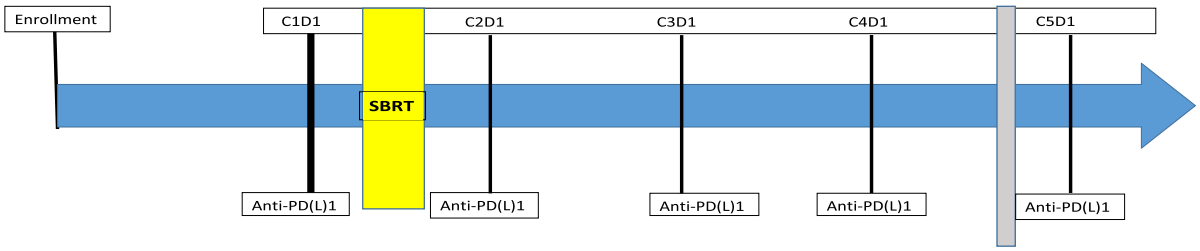

Figure 1: Study Schema. Abbreviations: Anti-PD(L)1=Pembrolizumab in this trial, Anti-PD(L1) Cycle Length= 3 weeks *Imaging will occur at week 12 +/- 7 days

STUDY SYNOPSIS

Title	FAST: Feasibility trial of Anti-PD(L)1 and SBRT in the Treatment of Advanced, Platinum-Refractory Urothelial Carcinoma
Phase	Feasibility
Methodology	Single Arm
Study Duration	12 months treatment, up to 24 months follow-up
Study Center(s)	University of Michigan
Objectives	**Primary Objective** To assess the feasibility of treating patients with sequential pembrolizumab and SBRT in patients with metastatic urothelial carcinoma who have progressed on platinum based chemotherapy **Secondary Objectives** 1) To determine the safety of the combination of SBRT and pembrolizumab in patients with platinum-refractory metastatic urothelial carcinoma 2) To determine the anti-tumor efficacy of the combination of SBRT and pembrolizumab in patients with platinum-refractory metastatic urothelial carcinoma **Exploratory Correlative Objectives** 1. To determine PD-L1 expression on tumor cells and tumor immune infiltrating cells in archival tumor specimens and correlate these findings with clinical outcomes 2. To evaluate the tumor mutational profile and burden by tissue based next generation sequencing (MI-Oncoseq) of fresh and/or archival tissue and correlate with clinical outcomes 3. To evaluate the tumor immune infiltrate of tumor tissue by gene expression profiling using CIBERSORT/TIMER and correlate these findings with clinical outcome
Number of Subjects	20

Inclusion Criteria	1. Subjects must have a histologic diagnosis of urothelial carcinoma. 2. Subjects must have radiologic evidence of metastatic disease with measurable disease by RECIST 1.1 criteria other than the target lesion(s) for SBRT. 3. Subjects must have at least 1 metastatic lesion previously not radiated that is amenable to SBRT per treating radiation oncologist. 4. Subjects must have had progression of disease within 12 months of platinum-containing chemotherapy (chemotherapy could have been given in the neoadjuvant, adjuvant or metastatic setting) for urothelial cancer 5. ECOG performance status of 0 to 2. 6. Absolute neutrophil count of ≥ 1000/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥ 8.0 g/dl; total bilirubin/ALT/AST < 2.5 x upper limit of normal (patients with known gilbert disease who have serum bilirubin ≤3x ULN may be enrolled); serum creatinine <3.0mg/dl or if elevated, a calculated estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m2 7. Subjects must have recovered to baseline or ≤ grade 1 CTCAE v 4.03 from toxicities related to any prior treatments unless AE(s) are clinically non-significant and/or stable on supportive therapy 8. Patients must be ≥ 2 weeks from most recent systemic therapy or most recent radiation therapy. 9. Women of childbearing potential must have a negative serum or urine pregnancy test within 28 days prior to registration. Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, are naturally postmenopausal for at least 12 consecutive months or have undergone surgical removal of the ovaries 10. Age ≥ 18 years
Key Exclusion Criteria	1. Prior treatment with anti-PD-1/PD-L1 and anti-CTLA-4 is NOT allowed. Prior intravesical BCG therapy is allowed. 2. Treatment with any investigational agent or on an interventional clinical trial within 30 days prior to treatment on protocol 3. No prior or concurrent malignancy is allowed except for: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, localized or locally advanced prostate cancer definitively treated without recurrence or with biochemical recurrence only, or any other cancer fully treated or from which the subject has been disease-free for at least 2 years. 4. Autoimmune diseases such as rheumatoid arthritis are NOT allowed. Vitiligo, mild psoriasis (topical therapy only) or hypothyroidism are allowed. 5. Need for systemic corticosteroids > 10mg prednisone daily or equivalent alternative steroid (except physiologic dose for adrenal replacement therapy) or other immunosuppressive agents (such as cyclosporine or methotrexate). Use of topical and inhaled corticosteroids is permitted. 6. Any history of organ allografts 7. Any history of HIV or hepatitis B infection 8. Known brain metastases
Study Product(s), Dose, Route, Regimen	• Pembrolizumab 200 mg IV q 21 days • Stereotactic body radiation therapy (SBRT) that will commence not later than the initiation of the second cycle of pembrolizumab. SBRT dose and fractionation will be at the discretion of the treating radiation oncologist, and will be selected to respect the

	normal tissue tolerance of adjacent organs at risk. The minimum dose will be 8 Gy for a 3-fraction course, or 6 Gy for a 5-fraction course.
Duration of Administration	• Patients will continue pembrolizumab until progression, toxicity, or a total of 17 cycles, whichever comes first • Patients will receive one course of SBRT on protocol. Further courses if clinically indicated are at discretion of treating physician
Reference Therapy	Pembrolizumab Monotherapy
Statistical Methodology	The primary aim of this study is to determine the feasibility of treating patients with metastatic urothelial carcinoma who have progressed after platinum based chemotherapy with sequential pembrolizumab and SBRT. Treatment success will be defined as completion of 4 cycles of pembrolizumab and at least one course of treatment of SBRT within 15 weeks from first dose of pembrolizumab. The trial will define the combination treatment as feasible if 70% of the patients receive the treatment as defined. With 20 evaluable patients, if 14 out of 20 (70% [95% Confidence Interval: 50% - 90%]) achieve successful treatment then the trial will conclude that further evaluation of sequential pembrolizumab and SBRT should be explored. A patient is evaluable for feasibility if they receive at least one dose of pembrolizumab. Patients who achieve a complete response prior to SBRT are not evaluable for feasibility. Non-evaluable patients will be replaced.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background Disease Background

Bladder cancer is the 4th most common malignancy in men [1]. While the majority of patients present with disease confined to the bladder, those who develop metastatic disease have a poor prognosis with an average overall survival of 15 months [2]. Regrettably, this statistic has not significantly changed over the past 15 years and the 5 year overall survival of patients with metastatic disease remains only 15% [3]. The current standard of care for metastatic urothelial carcinoma is a platinum containing chemotherapy regimen. Inevitably, most patients progress despite adequate chemotherapy.

Since 2016, several new drugs including pembrolizumab have been approved for the treatment of metastatic platinum refractory urothelial carcinoma (PRUC). Pembrolizumab works by inhibiting the interaction of programmed death ligand-1 (PD-L1) with its receptor, programmed death protein 1 (PD-1). By inhibiting this interaction, pembrolizumab may allow T cells to attack the tumor. Unfortunately, pembrolizumab only benefits a subset of patients as evidenced by the overall response rate of only 21% [4]. Given the potential for prolonged responses with immunotherapy, there is an urgent unmet clinical need for combination therapies that increase the response rate to immunotherapy.

1.2 Study Agent(s) Background and Associated Known Toxicities

Pembrolizumab
Pembrolizumab is a monoclonal antibody designed to bind to PD-1. Pembrolizumab received accelerated approval for the treatment of platinum refractory urothelial carcinoma as a result of findings from KEYNOTE-045, a multicenter, randomized trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. Patients were randomly assigned (1:1) to receive either pembrolizumab 200 mg every 3 weeks (n=270) or investigator's choice of a chemotherapy regimen (paclitaxel [n=84], docetaxel [n=84], or vinflunine [n=87]) every 3 weeks (n=272). The trial demonstrated statistically significant improvements in overall survival (OS) and objective response rate (ORR) for patients assigned to pembrolizumab as compared to chemotherapy. Median OS was 10.3 and 7.4 months in the pembrolizumab and chemotherapy arms, respectively (HR 0.73; 95% CI: 0.59, 0.91, p=0.004). ORR was 21% for pembrolizumab and 11% for chemotherapy (p=0.002). No statistically significant difference in progression-free survival between the two arms was observed [4].

Stereotactic Body Radiation Therapy (SBRT)

The addition of radiation to immunotherapy has shown promise in the pre-clinical setting. Radiation has long been known to be tumoricidal by inducing local DNA breaks. Recent research has shown that radiation affects the tumor immune microenvironment as well. In the pre-clinical setting, radiation has been shown to decrease the frequency of immunosuppressive myeloid derived suppressor cells (MDSCs) [5] and lead to an increased frequency of CD8 positive T cells in both the tumor and tumor draining lymph nodes [6].

Additionally, the way in which radiation is delivered has differential effects on the immune system. For example, some studies have shown that low dose conventional fractionated therapy (as compared to ablative, hypofractionated therapy) is in part immunosuppressive by continuously killing off effector T cells alongside tumor cells [7].

Despite these beneficial immuno-modulating effects, radiation has some immunosuppressive effects as well. Radiation has been shown to increase the number of

immunosuppressive T-regulatory (Treg) cells in the tumor immune infiltrate [8] as well activate the immunosuppressive cytokine TGFβ [9]. While the overall effect of radiation is felt to be immune-stimulatory, radiation alone typically does not induce a potent enough immune response to incite systemic tumor responses. However, if combined with a systemic therapy such as anti-PD1 checkpoint immunotherapy, the radiation-induced immune effects have the potential to be synergistic and robust.

1.3 Rationale

Several pre-clinical studies have analyzed the impact of combining radiation and checkpoint inhibitors. In a study by Deng et al, the addition of an anti-PDL1 antibody led to a 15 fold reduction in intra-tumoral MDSCs as compared to radiation alone [5]. This local reduction in MDSCs was associated with enhanced tumor growth delay and tumor regression. In another study, radiation was combined with an anti-CTLA4 immunotherapeutic agent and given at various time intervals. Mice who received the anti-CTLA4 drug prior to radiation had significantly more tumor regression than those who received the anti-CTLA4 drug after radiation [10], suggesting an ongoing immune-facilitatory milieu enhances radiation's impact.

In addition to focal immune effects at the site of the irradiated tumor lesion, radiation can lead to a decrease in size of distant tumor lesions as well, presumably via an immune mediated mechanism, sometimes known as the abscopal effect. The abscopal effect is a phenomenon wherein local therapy is associated with the regression of metastatic cancer at a distance from the site treated with local therapy (See Figure 2). One hypothesis is that the local therapeutic effect is amplified by a body-wide immune response. This effect was demonstrated in work by Demaria et al in which mice treated with local radiation and a CTLA-4 antibody had a reduction in distant lung metastases and an improved overall survival as compared with mice treated with the CTLA-4 antibody or radiation alone. [11]. The abscopal effect has also been well documented in humans [12].

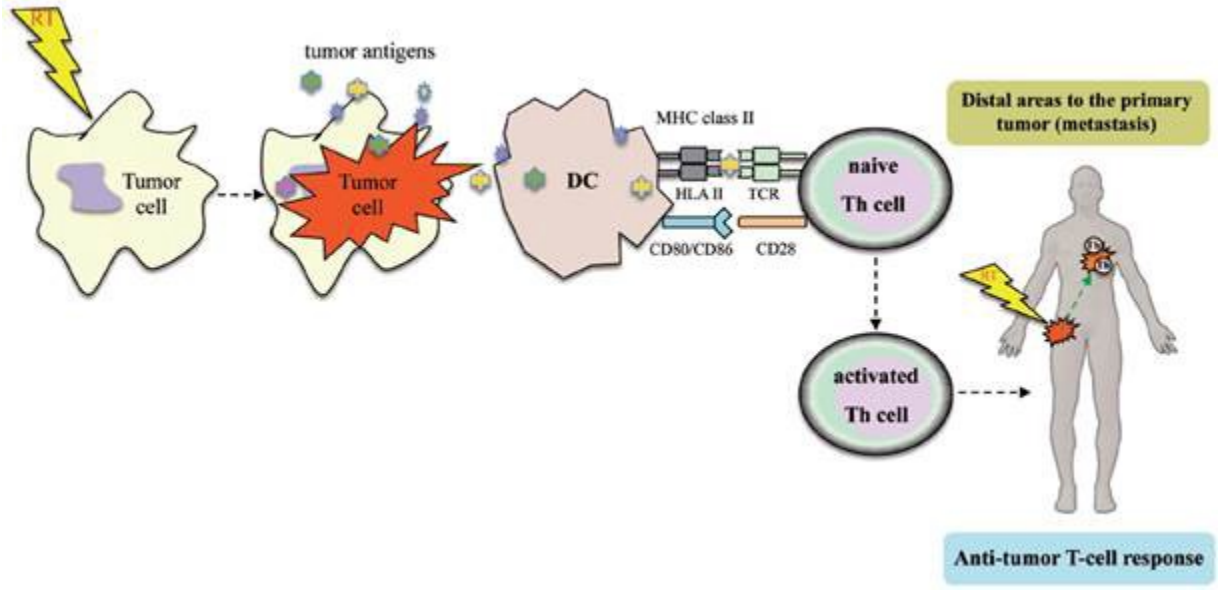

Figure 2: Representation of presumed mechanism of the abscopal effect [13]. Abbreviations: DC, dendritic cell; HLA: human leukocyte antigen; MHC: major histocompatibility complex; RT: radiation therapy; TCR: T cell receptor; Th: T helper

Pre-clinical studies have clearly demonstrated a benefit to the combination of radiation and immunotherapy. However, the mechanism by which this combination is immune-stimulatory has not been fully elucidated. The prevalent basic hypothesis is that radiation leads to increased tumor antigen release translating to a stronger immune reaction when subsequently treated with immunotherapeutic drugs. While this is a plausible hypothesis,

it has not been extensively evaluated in patients treated with new immunotherapies and new forms of radiation such as stereotactic body radiation therapy (SBRT). In a small phase one study, the combination of Interleukin-2 (IL-2) and SBRT led to a substantially improved response rate compared to historical controls in patients with melanoma and kidney cancer [14]. Case reports have shown similar responses with newer immunotherapy drugs such as ipilimumab, an anti-CTLA4 drug [12]. Given these encouraging results, the concept of combining SBRT with immunotherapy warrants further evaluation with newer immunotherapeutics such as pembrolizumab that are more widely applicable than IL-2.

We propose a single-center feasibility trial to study the combination of SBRT with pembrolizumab in patients with metastatic urothelial carcinoma who have progressed on or within 12 months of platinum based chemotherapy. One dose of pembrolizumab will be given followed by SBRT to at least 1 amenable lesion chosen at the discretion of the radiation oncologist. This will be followed by three further cycles of pembrolizumab before the patient is assessed radiographically. Subjects must have RECIST 1.1 measurable disease in addition to the lesion proposed to be treated with SBRT.

1.4 Correlative Studies

Correlative studies comprehensively evaluating the tumor immune profile and mutational profile will be performed as described below. We plan to evaluate the following:

1) Evaluation of PD-L1 expression on the tumor cells and tumor infiltrating lymphocytes and correlation of these levels with clinical response to treatment

In the IMvigor 210 trial, PD-L1 expression on immune cells infiltrating tumor tissue did correlate with response. Twenty-six percent of patients whose tumor immune cells were highly positive by IHC responded whereas only 8% of patients whose tumor immune cells were PDL1 negative had a response. While displaying an important trend, PD-L1 expression is not a perfect biomarker, as evidenced by the fact that 2% of patients in the PD-L1 negative group had a complete response to atezolizumab [15].

2) Evaluate tumor mutational profile and burden by tissue based next generation sequencing (MI-Oncoseq) and correlate with clinical outcomes

Recent studies have shown that tumor mutational burden may predict for response to checkpoint inhibitors with a higher mutational load corresponding to improved efficacy. [16], [17]. In addition, specific mutations may predict for improved responses to immunotherapy as evidenced by the improved survival seen in patients with mismatch repair deficient colon cancer treated with pembrolizumab [18]. We will co-consent subjects to the University of Michigan tumor sequencing protocol MI-Oncoseq. Fresh and/or archival tumor tissue and germline tissue will undergo genomic profiling. We will also offer patients an optional biopsy at progression to look for changes in the tumor genome.

3) Evaluation of the tumor immune infiltrate by gene expression profiling (CIBERSORT)/TIMER) using RNASeq data

While the tumor immune environment is often characterized by IHC analysis, it is also possible to evaluate the tumor immune environment with gene expression profiling. In a recent publication by Newman et al, they describe a technique called CIBERSORT (Cell-type Identification by Estimating Relative Subsets of RNA Transcripts) [19]. This is a technique that combines gene expression profiling with a complex computational method that can identify the relative fractions of immune cell subsets in tumor tissue. This technique correlated well with flow cytometry but has not been extensively evaluated clinically. It is possible this technique could be superior to standard evaluation by immunohistochemistry (IHC) due to the limited repertoire of phenotypic

markers used for classification of the immune infiltrate by IHC. As a subproject of OncoSeq analysis, we will analyze gene expression profiles using next generation sequencing based computational methods that accurately resolves relative fractions of various cell subsets using CIBERSORT/TIMER. We will obtain tumor tissue and explore an analysis of the tumor immune infiltrate by CIBERSORT. We will explore correlation between the CIBERSORT/TIMER data and clinical outcomes.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

1. To assess the feasibility of treating patients with sequential pembrolizumab and SBRT in patients with metastatic urothelial carcinoma who have progressed on platinum based chemotherapy

2.2 Secondary Objectives

1. To determine the safety of the combination of SBRT and pembrolizumab in patients with platinum-refractory metastatic urothelial carcinoma.
2. To determine the anti-tumor efficacy of the combination of SBRT and pembrolizumab in patients with platinum-refractory metastatic urothelial carcinoma.

2.3 Correlative Objectives

1. To determine PD-L1 expression on tumor cells and tumor immune infiltrating cells in archival tumor specimens and correlate these findings with clinical outcomes
2. To evaluate the tumor mutational profile and burden by tissue based next generation sequencing (MI-Oncoseq) of fresh and/or archival tissue and correlate with clinical outcomes.
3. To evaluate the tumor immune infiltrate of tumor tissue by gene expression profiling using CIBERSORT/TIMER and correlate these findings with clinical outcome.

2.4 Endpoints

Primary Endpoint

1. Proportion of subjects who receive 4 doses of pembrolizumab and at least one session of treatment of SBRT within 15 weeks from the first dose of pembrolizumab.

Secondary Endpoints

1. Frequency and severity of Grade 3-5 drug-related adverse events graded by CTCAE v4.30.
2. Overall response proportion (Best Overall Response) and Progression Free Survival by RECIST, and Immune Related Response Criteria.

3.0 PATIENT ELIGIBILITY

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

3.1 Inclusion Criteria

3.1.1 Subjects must have a histologic diagnosis of urothelial carcinoma

3.1.2 Subjects must have radiologic evidence of metastatic disease with measurable disease by RECIST 1.1 criteria other than the target lesion(s) for SBRT

3.1.3 Subjects must have at least 1 metastatic lesion previously not radiated that is amenable to SBRT per treating radiation oncologist.

3.1.4 Subjects must have had progression of disease within 12 months of platinum-containing chemotherapy (chemotherapy could have been given in the neoadjuvant, adjuvant or metastatic setting) for urothelial cancer

3.1.5 ECOG performance status of 0 to 2

3.1.6 Absolute neutrophil count of ≥ 1000/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥ 8.0 g/dl; total bilirubin/ALT/AST < 2.5 x upper limit of normal (patients with known gilbert disease who have serum bilirubin ≤3x ULN may be enrolled); serum creatinine <3.0mg/dl or if elevated, a calculated estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m2

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

3.1.8 Subjects must be ≥ 2 weeks from most recent systemic therapy or most recent radiation therapy

3.1.9 Women of childbearing potential must have a negative serum or urine pregnancy test within 28 days prior to registration. Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, are naturally postmenopausal for at least 12 consecutive months or have undergone surgical removal of the ovaries. Women of childbearing potential should use highly effective contraception during treatment and for 6 months after the last dose of pembrolizumab

3.1.10 Age ≥ 18 years

3.2 Exclusion Criteria

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

3.2.2 Treatment with any investigational agent or on an interventional clinical trial within 30 days prior to registration.

3.2.3 No prior or concurrent malignancy is allowed except for: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, localized or locally advanced prostate cancer definitively treated without recurrence or with biochemical recurrence only, or any other cancer fully treated or from which the subject has been disease-free for at least 2 years.

3.2.4 Autoimmune diseases such as rheumatoid arthritis are NOT allowed. Vitiligo, mild psoriasis (topical therapy only) or hypothyroidism are allowed

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

3.2.6 Any history of organ allografts

3.2.7 Any history of HIV or hepatitis B infection

3.2.8 Known brain metastases

3.2.9 Patients who are pregnant or breast feeding

3.2.10 Patients with a history of thoracic radiation of dose > 30 Gy within the prior 26 weeks

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

After informed consent is obtained and PRIOR to the initiation of protocol therapy all patients satisfying the inclusion/exclusion criteria must have eligibility confirmed by the Oncology Clinical Trials Support Unit (OCTSU). The patient will not be considered registered and enrolled in the study until all information is confirmed by the OCTSU Data Manager.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

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

5.1.1 Therapy will include pembrolizumab 200 mg IV starting on day 1 in 21 day cycles. Patients will receive 1 dose (cycle 1) of pembrolizumab and commence SBRT no later than initiation of cycle 2.

5.1.2 SBRT will be given to ≥ 1 metastatic lesion(s) deemed most appropriate for such therapy by the treating radiation oncologist. SBRT will be delivered in 3 or 5 fractions with dose and fractionation selected to respect standard normal tissue dose constraints for adjacent organs at risk. See section 5.3 for further details.

5.1.3 The lesion to which SBRT is given will be identified after the patient receives 1 dose of pembrolizumab

5.1.3 Patients will be treated with supportive care pre-medications as clinically indicated including anti-emetics.

REGIMEN DESCRIPTION					
Agent	**Premedications**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pembrolizumab	None mandated	200 mg	IV	Once every 21 days (+/- 3 business days)	
SBRT	None mandated	3-5 fractions with dose and fractionation selected to respect standard normal tissue dose constraints for the relevant organs in the vicinity of the target lesion(s).	n/a	In cycle 1 any time after D1 and will commence no later than initiation of cycle 2	

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives one dose of pembrolizumab will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Dose modifications in strength are not permitted for pembrolizumab

Dosing delays for Pembrolizumab:

- No dose delays for pembrolizumab are needed for hematologic changes.

- With any grade 2 or higher **non-hematologic toxicity deemed to be related to pembrolizumab**, hold pembrolizumab and refer to section 5.2.1. If adverse event is not an event of interest and improves to grade 1 or better, pembrolizumab may be resumed.
- If non-hematologic toxicity does not improve to grade 1 or better in 12 weeks from prior dose, discontinue pembrolizumab.

5.2.1 Events of interest for Pembrolizumab:

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

5.2.1.1 Pulmonary:

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

Grade of pneumonitis (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 Radiographic Changes Only	• Consider delay of pembrolizumab • Monitor for symptoms every 2-3 days • Consider pulmonary and infectious disease consultations	• Re-image at least every 3 weeks • If worsening, treat as grade 2, 3 or 4

Grade 2
Mild to moderate new symptoms
	• Delay pembrolizumab
	• Consult pulmonary and infectious disease
	• Monitor symptoms daily, consider hospitalization
	• 1.0mg/kg/day methylprednisolone IV or oral equivalent
	• Consider bronchoscopy and/or lung biopsy
		• Re-image every 1-3 days
		• Consider prophylactic antibiotics while on steroids
		• If improves:
		  • When symptoms return to near baseline, taper steroids over at least one month
		  • When steroids are at 10mg oral prednisone (or equivalent) or below, resume pembrolizumab
		• If not improving after 2 weeks or worsening, treat as grade 3 or 4

Grade 3 or 4
Severe new symptoms and/or new or worsening hypoxia
	• Discontinue pembrolizumab
	• Hospitalize
	• Consult pulmonary and infectious disease
	• 1-2mg/kg/day methylprednisolone IV or IV equivalent
	• Add prophylactic antibiotics for opportunistic infections like PCP
	• Consider bronchoscopy and/or lung biopsy
		• If improves to baseline:
		  • Taper steroids for at least 6 weeks
		• If not improving after 48 hours or worsening
		  • Add additional immunosuppressive agent(s) (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin or

		mycophenolate mofetil)

5.2.1.2 Gastrointestinal:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Opiates or narcotics may mask symptoms of perforation. Infliximab should not be used in case of perforation or sepsis.

Grade of diarrhea/colitis (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 • Diarrhea of less than 4 stools per day over baseline or asymptomatic colitis	• Continue pembrolizumab • Symptomatic treatment such as loperamide	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately • If worsening, treat as grade 2,3 or 4
Grade 2 • Diarrhea of 4-6 stools per day over baseline OR • IV fluids needed < 24 hours due to diarrhea OR • Colitis with abdominal pain or blood in stool	• Delay pembrolizumab Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) • Consider prophylactic antibiotics for opportunistic infections like PCP if steroid treatment prolonged •	• If improves to grade 1, resume pembrolizumab • Resume pembrolizumab if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10mg oral prednisone per day • When symptoms improve to grade 1, taper steroids over at least one month • If worsening, treat as grade 3 or 4

Grade 3
• Diarrhea ≥ 7 stools per day over baseline
OR
• IV fluids needed for ≥ 24 hours due to diarrhea
OR
• Colitis with severe abdominal pain or medical intervention indicated
	• Delay pembrolizumab
	• 1-2mg/kg/day methylprednisolone IV or IV equivalent
	• Start prophylactic antibiotics for opportunistic infections such as PCP
	• Consider lower endoscopy
		• If improves
		  • Continue steroids until symptoms are grade 1, then taper over at least one month
		  • Resume pembrolizumab if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10mg oral prednisone per day
		• If persists for >3-5 days or recurs after improvement, add infliximab 5mg/kg if no contraindication (Note: infliximab should not be used in cases of perforation or sepsis)

Grade 4 Life threatening or perforation	• Discontinue pembrolizumab • 1-2mg/kg/day methylprednisolone IV or IV equivalent • Start prophylactic antibiotics for opportunistic infections such as PCP • Consider lower endoscopy	• If improves • Continue steroids until symptoms are grade 1, then taper over at least one month • If persists for >3-5 days or recurs after improvement, add infliximab 5mg/kg if no contraindication (Note: infliximab should not be used in cases of perforation or sepsis)

5.2.1.3 Endocrinopathy:

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

Endocrinopathy	Management	Follow-up
Asymptomatic thyroid-stimulating hormone (TSH) elevation	• Continue pembrolizumab • If TSH <0.5 x LLN or TSH >2x ULN, or consistently out of range in subsequent measurements, include free T4 in subsequent measurements as clinically indicated • Consider endocrinology consult	
Symptomatic Hypothyroidism	• Initiate thyroid replacement	
Symptomatic Hyperthyroidism	• Delay pembrolizumab • Consider endocrinology consult • Initiate anti-thyroid drug	• Resume pembrolizumab when symptoms of hyperthyroidism are controlled and thyroid function is improving
Hypophysitis	• Administer corticosteroids and hormone replacement as clinically indicated • Delay pembrolizumab for grade 2 or 3 hypophysitis • Permanently discontinue pembrolizumab for grade 4 hypophysitis	
Symptomatic Adrenal Insufficiency	• Delay pembrolizumab • Administer methylprednisolone 1-2 mg/kg/day IV followed by oral prednisone 1-2mg/kg per day or equivalent once symptoms improve • Add prophylactic antibiotics for opportunistic infections	• If improves to ≤ grade 1, taper steroids over at least one month • Resume pembrolizumab if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤10 mg oral prednisone per day and the patient is on stable replacement therapy if required

5.2.1.4 Hepatic:

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

Grade of Liver Test Elevation (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 AST or ALT >ULN to 3x ULN and/or total bilirubin >ULN to 1.5x ULN	• Continue pembrolizumab	• Continue liver function test monitoring per protocol • If worsening, treat as grade 2,3, or 4
Grade 2 AST or ALT >ULN to 3-5x ULN and/or total bilirubin >ULN to 1.5-3x ULN	• Delay pembrolizumab • Administer corticosteroids at a dose of 1-2mg/kg/day oral prednisone	• Resume pembrolizumab if returns to baseline • If persists >5-7 days or worsens, treat as grade 3 or 4

Grade 3 or 4
AST or ALT >5x ULN and/or total bilirubin >3x ULN
	• Discontinue pembrolizumab
	• Increase frequency of monitoring to every 1-2 days
	• 1-2mg/kg/day methylprednisolone IV or IV equivalent for grade 3 and 2 mg/kg/day methylprednisolone IV for grade 4
	• Add prophylactic antibiotics for opportunistic infections like PCP
	• Consult gastroenterologist
		• If improves to grade 2, taper steroids over at least one month
		• If does not improve within 3-5 days or worsens after improvement:
		  • Add mycophenolate mofetil 1g twice daily
		  • If no response within an additional 3-5 days, consider other immunosuppressive agents per local guidelines

5.2.1.5 Pancreatic:

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

Grade of pancreatic toxicity (NCI CTCAE v4.03)	Management	Follow-up
Grade 1-2 Amylase or Lipase up to 2x ULN	• Continue pembrolizumab	
Grade 2 or 3 Pancreatitis or Grade 3 serum amylase or lipase level (>2x ULN)	• Delay or pembrolizumab • Treat with 1-2mg/kg IV methylprednisolone or equivalent per day	• Once symptoms improve, follow with 1-2mg/kg of oral prednisone or equivalent per day • Resume pembrolizumab if amylase/lipase improves to ≤ grade 1 within 12 weeks, symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day
Grade 4 or recurrent pancreatitis	• Discontinue pembrolizumab • Treat with 1-2mg/kg IV methylprednisolone or equivalent per day	• Once symptoms improve, follow with 1-2mg/kg of oral prednisone or equivalent per day and taper for ≥ 1 month

5.2.1.6 Neurological:

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

Grade of neurological toxicity (NCI CTCAE v 4.03)	Management	Follow-up
Grade 1 • Asymptomatic or mild symptoms • Intervention not indicated	• Continue pembrolizumab	• Continue to monitor the patient, if worsening treat as grade 2, 3, or 4

Grade 2 • Moderate symptoms • Limiting instrumental ADLs	• Delay pembrolizumab • Treat symptoms per institutional guidelines • Consider 0.5-1mg/kg per day methylprednisolone IV or oral equivalent	• If returns to baseline, resume pembrolizumab • If worsens, treat as grade 3 or 4
Grade 3 or 4 • Severe symptoms • Limiting self-care ADLs	• Discontinue pembrolizumab • Consult Neurology • Treat symptoms per institutional guidelines • 1-2mg/kg per day IV methylprednisolone or IV equivalent • Add prophylactic antibiotics for opportunistic infections	• If improves to grade 2, taper steroids over at least one month • If worsens, consider IVIG or other immunosuppressive therapies per institutional guidelines
Meningitis or Encephalitis	• Discontinue pembrolizumab • 1-2mg/kg per day IV methylprednisolone or IV equivalent • Add prophylactic antibiotics for opportunistic infections	• If improves, convert to oral steroids (prednisone 60mg/day or equivalent) • When symptoms improve to ≤ grade 1, taper steroids over at least one month

5.2.1.6 Skin:

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

Grade of Rash (NCI CTCAE v4.03)	Management	Follow-up

Grade 1-2
Covering ≤ 30% body surface area (BSA)
	• Symptomatic therapy (such as antihistamines, topical steroids)
	• Continue pembrolizumab
		• If persists 1-2 weeks or recurs
		  • Consider skin biopsy
		  • Delay pembrolizumab
		  • Consider 0.5-1mg/kg/day methylprednisolone IV or oral equivalent
		  • Once improving, taper steroids for at least one month
		  • Consider prophylactic antibiotics for opportunistic infections like PCP
		  • Resume pembrolizumab if rash improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day
		• If worsens, treat as grade 3 or 4

Grade 3-4
Covering >30% BSA or life threatening consequences
	• Delay or discontinue pembrolizumab
	• Consider skin biopsy
	• If patient is diagnosed with Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN), pembrolizumab must be discontinued
	• Consult dermatology
		• If improves to grade 1:
		  • Taper steroids over at least one month
		  • Resume pembrolizumab if rash improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day

	• 1-2mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	

5.2.1.7 Renal:

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

Grade of elevation in serum creatinine (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 Serum creatinine >ULN and >baseline but ≤1.5x baseline	• Continue pembrolizumab • Monitor serum creatinine weekly	• If returns to baseline, resume creatinine monitoring per protocol • If worsens, treat as grade 2, 3, or 4

Grade 2 or 3
Serum creatinine 1.5x baseline to ≤ 6 x ULN
	• Delay or discontinue pembrolizumab
	• Monitor serum creatinine every 2-3 days
	• 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent
	• Add prophylactic antibiotics for opportunistic infections
	• Consider renal biopsy
		• If improves to grade 1
		  • Taper steroids over at least one month
		  • Resume pembrolizumab if improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day
		• If elevation persists >7 days or worsens, treat as grade 4

Grade 4
Serum creatinine <6x ULN
	• Discontinue pembrolizumab
	• Monitor serum creatinine daily
	• 1-2mg/kg/day methylprednisolone IV or IV equivalent
	• Add prophylactic antibiotics for opportunistic infections
	• Consult nephrology
	• Consider renal biopsy
		• If improves to grade 1
		  • Taper steroids over at least one month
		  • Resume pembrolizumab if improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day

5.2.1.8 Infusion Related Reactions

Pembrolizumab can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving Pembrolizumab.

Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue pembrolizumab

5.3 Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) involves advanced planning and delivery techniques to administer ablative doses of radiation to a target in a small number of fractions (treatment sessions). This has radiobiologic advantages and has been shown to be safe in numerous settings. A high priority is placed on minimizing exposure to surrounding normal tissues. Patients on this protocol will receive between three and five fractions of treatment. The dose per fraction will be determined per standard clinical practice and will be dependent on the location of the treated site and the adjacentorgans at risk. SBRT will commence no later than initiation of the second cycle of pembrolizumab.

Both 3D-conformal radiotherapy and intensity-modulated radiotherapy (including volumetric arc radiotherapy [VMAT]) are acceptable planning techniques. Daily image guidance is required for this study.

5.3.1 Dose and Fractionation

The 3-fraction regimen will employ a minimum fraction size of 8 Gy and the 5-fraction regimen will employ a minimum fraction size of 6 Gy. Dose and fractionation will be determined per standard clinical practice and will be dependent on the location of the treatment site and adjacent organs at risk (i.e. to respect normal tissue tolerances).

Dose rate: For the purposes of this protocol, dose rate will be that which is commissioned by the manufacturer and the medical physics group for external beam radiotherapy delivery by the University of Michigan. There will be no special dose rate modifications required for this study.

5.3.2 Localization, Simulation, and Immobilization

Patients will be immobilized in an appropriate position to isolate the target lesion and will then undergo CT-based treatment planning. The CT scan must capture the region of interest as well as surrounding organs at risk (OAR) with adequate margin for treatment planning. The CT scan should be obtained with a uniform slice thickness of less than or equal to 3 mm. The use of IV contrast is at the discretion of the treating physician.

All lesions with the potential for respiratory motion should be evaluated by appropriate means, such as with a 4D-CT scan and/or implanted beacon(s)/marker(s). Respiratory motion management, including—but not limited to—methods such as breath hold, respiratory gating, and fiducial marker tracking, will be employed for applicable patients per standard clinical practice.

Daily image guidance will be employed for target localization. Typically this will include volumetric imaging (cone-beam CT) when possible, as well as any additional techniques deemed helpful.

5.3.3 Target Volumes

The gross tumor volume (GTV) is defined as all known gross disease corresponding to the selected lesion as visualized on the planning CT scan and aided by any additional relevant imaging studies (e.g. additional CT scans, PET/CT, MRI, etc.). The use of additional diagnostic imaging studies is dependent on the location of the lesion and is left to the discretion of the treating physician. An internal target volume (ITV) is defined for mobile lesions at the discretion of the treating physician. A 4D-CT scan will be acquired in order to account for the motion of the lesion if necessary. Breath hold techniques are also acceptable. For moving lesions, the ITV will be defined as the union of the visualized lesion on all gated CT datasets.

The clinical target volume (CTV) will equal the GTV/ITV with additional margin added to account for subclinical disease extension where appropriate as per standard practice. In the case of a lung metastasis, for example, the CTV would generally be equal to the GTV/ITV, whereas for a bone metastasis a margin may be added to account for disease that may extend further into the marrow than visible on imaging.

The planning target volume (PTV) will be defined as per the convention for photon beam radiotherapy. A 3-dimensional margin will be created on the CTV to allow for daily set-up variation.

5.3.4 Normal Structures

Organs at risk (OARs) in the vicinity of the target lesion will be delineated as visualized on the planning CT scan. When applicable, an expansion of 1-5 mm may be used to generate a planning organ-at-risk volume (PRV) to account for setup uncertainty and motion.

5.3.5 Treatment Planning

Acceptable planning techniques include 3D-conformal radiotherapy and intensity-modulated radiotherapy (including volumetric arc radiotherapy [VMAT]). For 3D-conformal radiotherapy, static 3D coplanar and/or non-coplanar beam arrangements as well as dynamic conformal arcs are permitted.

In the case of 3D coplanar or non-coplanar beam arrangements, these plans will be customized for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are frequently advantageous. Often, ≥ 7-10 beams of radiation will be used with roughly equal weighting. More beams are typically used for larger lesion sizes. When static beams are used, a minimum of 7 non-opposing beams is encouraged. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) is encouraged.

In order to obtain acceptable coverage for 3D conformal techniques, field aperture size and shape should generally correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). An exception should be when observing the minimum field dimension when treating small lesions. As such, prescription lines covering the PTV will typically be the 60-90% line for 3D conformal plans (where the maximum dose is 100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The treatment isocenter or setup point in stereotactic coordinates will be determined from system fiducials (and can be adjusted pre-treatment depending on the results from localization imaging studies) and translated to the treatment record.

All dose calculations will include corrections for tissue heterogeneities as specified by IROC Houston.

Maximum Dose:
The treatment plan should be created such that the maximum point dose (to a volume of at least 0.03cc) is ≤130% of the prescription dose. This point must exist within the PTV.

Prescription Isodose:
This is variable, but for 3D conformal plans the prescription isodose surface will typically be 60-90% of the maximum dose.

Prescription Isodose Surface Coverage:

The prescription isodose surface will, ideally, be chosen such that ≥95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V(Rx dose in Gy) ≥95%) and ≥99% of the PTV receives a minimum of 90% of the prescription dose (PTV V(90%Rx dose in Gy) ≥99%). Additionally, every effort should be made to ensure that 100% of the GTV/ITV should receive≥100% of the Rx dose when possible. However, target coverage will be a priority 2 planning goal, and will therefore be secondary to priority 1 goals for critical organs at risk.

(i) High dose spillage: The cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the PTV volume. Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose to the volume of the PTV is ideally < 1.2. This may not be possible for very small tumors (< 2.5 cm axial CTV dimension or < 1.5 cm craniocaudal CTV dimension) due to the required minimum field size.

(ii) Intermediate dose spillage: The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and should ideally meet the following (suggested) criteria:

Location:
The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction should be no greater than D_{2cm} where D_{2cm} is given by the table below.

Volume:
The ratio of the volume of the 50% isodose volume to the volume of the PTV ($R_{50\%}$) should meet the criteria in the table below if possible (adapted from RTOG 0915), although in some cases this may not be achievable. This table is used for all prescription requirements irrespective of calculation algorithm and total treatment dose.

Table 1: Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)	
	Ideal	Good	Ideal	Good	Ideal	Good
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0

Critical Organ Doses:

Critical organ dose-volume limits with be those used in standard practice at the University of Michigan.

Planning Priorities:
Every attempt will be made to successfully satisfy all of the planning goals and OAR criteria. In some circumstances, it may not be possible to meet all the ideal criteria. In these cases, spinal cord, cauda equina, sacral plexus (when applicable), and brachial plexus dose constraints must be respected over PTV coverage. In the case of other OAR constraints, which are not well validated, PTV coverage and OAR constraints must be balanced per clinical practice at the discretion of the treating physician.

5.4 Concomitant Medications/Treatments

Systemic corticosteroids greater than the equivalent of 10mg of prednisone or equivalent alternative steroid (except physiologic dose for adrenal replacement therapy) or other immunosuppressive agents (such as cyclosporine or methotrexate) and any other medications that could potentially impact the efficacy or safety of the study as judged by the treating investigator are NOT permitted from time of registration to subjects completing protocol therapy unless clinically indicated to manage adverse events or life threatening or serious conditions as determined by the treating investigator.
Additional palliative radiation for pain, bleeding, airway compromise, or other needs is permitted.

5.5 Other Modalities or Procedures

Pembrolizumab should be held for any surgery until subject is judged to be stable to resume by treating investigator as adequate information does not exist on its effects on wound healing. When resumed, same dose level will be maintained. Percutaneous procedures like imaging guided biopsies and central line placements do not require pembrolizumab to be held.

5.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment will continue for 17 cycles or until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Patients may continue on pembrolizumab beyond the first progression by imaging as long as investigator deemed clinical benefit continues
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s) or death
- Patient voluntarily withdraws from treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.7 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.6 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.8. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.8 Duration of Follow-Up

Continued follow-up after end of treatment is for patients who discontinue study treatment for reasons other than progressive disease or death (such as patients who discontinue treatment due to toxicity) AND patients who continue on treatment past 17 cycles. These patients should continue to be followed by imaging every 12 weeks with standard of care CT chest, abdomen/pelvis until documentation of progressive disease, death, withdrawal of consent, or initiation of a new anti-cancer treatment for up to 2 years.

5.9 Off Study Criteria

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

- Patient withdraws consent (termination of treatment and follow-up);
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- Patient is unable to comply with protocol requirements;
- Treating physician judge's continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- 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;
- Lost to Follow-up. *If a research subject cannot be located to document progression free survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.*
- Termination of the study by The University of Michigan;
- Patient completes protocol treatment and follow-up criteria.

5.10 Patient Replacement

A patient is evaluable for feasibility and safety if they receive at least one dose of pembrolizumab. Patients who achieve a complete response prior to SBRT are not evaluable for feasibility. Non-evaluable patients will be replaced.

6.0 STUDY PROCEDURES

6.1 Follow-Up Procedures

Continued follow-up after end of treatment is for patients who discontinue study treatment for reasons other than progressive disease or death (such as patients who discontinue treatment due to toxicity) AND patients who continue on treatment past 17 cycles. These patients should continue to be followed by imaging every 12 weeks with standard of care CT chest, abdomen/pelvis until documentation of progressive disease, death, withdrawal of consent, or initiation of a new anti-cancer treatment for up to 2 years.

6.2 Time and Events Table

All assessments have a window of ± 5 business days except for imaging/tumor measurements where a window of ± 7 business days will apply.

Study Calendar

	Screening period (within 28 days)	C1 D1 [1]	SBRT (will commence no later than initiation of cycle 2)[3]	C2 D1	C3 D1	C4 D1	Week 12	C5 D1	Cycles per std frequency for drug	Every 12 weeks	End of Treatment	Follow-up (every 12weeks for up to 24 months[5]
Informed Consent for FAST	X											
Informed Consent for MI-Oncoseq[4]	X											
Archival Tissue identified	X											
Serum and Plasma banking	X[2]											
Optional Biopsy at Progression											X	
History and Physical	X	X		X	X	X		X	X		X	
ECOG PS	X	X		X	X	X		X	X		X	
Tumor Measurements	X						X			X		X
Toxicity Evaluation	X	X		X	X	X		X	X		X	
CBC with diff and platelet count	X	X		X	X	X		X	X		X	
Comp metabolic panel	X	X		X	X	X		X	X		X	
Amylase/Lipase	X							X		X	X	
TSH, free T3, free T4 (IF clinically indicated: FSH, LH, ACTH)	X							X		X	X	
HIV, Hepatitis B Surface Antigen	X											
Pregnancy test for WOCBP	X											
CT Chest	X						X			X		X

CT or MRI Abdomen/Pelvis	X						X			X		X
Pembrolizumab		X		X	X	X		X	X			
SBRT			X									

[1]Cycles are 21 days in duration.
[2] Serum and plasma banking will be collected C1D1 prior to first dose
[3]SBRT cannot overlap with C1D1
[4]Optional
[5] Continue follow-up after end of treatment is for patients who discontinue study treatment for reasons other than progressive disease or death AND patients who continue on treatment past 17 cycles. These patients should continue to be followed by imaging every 12 weeks with standard of care CT chest, abdomen/pelvis until documentation of progressive disease, death, withdrawal of consent, or initiation of a new anti-cancer treatment for up to 2 years.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

Definitions

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

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

Disease Parameters

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

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

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

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

Guidelines for Evaluation of Measurable Disease

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin

nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

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

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

Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.				

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

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

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.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Patients without progression or death will be censored at the date of their last scan.

7.2 Immune Related Response Criteria

As a secondary endpoint, this study will evaluate concordance of the Immune Related Response Criteria (irRC) with RECIST 1.1. These response criteria were developed to overcome the variable and unusual patterns of response to immunotherapeutic agents, in particular, ipilimumab. The development of the guidelines was prompted by observations, mostly in subjects with metastatic melanoma, of initial disease progression followed by later response, late responses, and mixed responses with an overall decrease in tumor burden.

Antitumor response based on total measurable tumor burden

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden:

Tumor Burden = SPDindex lesions + SPDnew, measurable lesions

Table: Comparison of WHO and irRC criteria

	WHO	irRC
New, measurable lesions	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Time-point response assessment using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same. However, the irRC response categories have been modified from those of WHO criteria.

Overall response using the irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the 2 largest perpendicular diameters of all

index and all new measurable lesions (ie, Percentage Change in Tumor Burden). **Note:** the appearance of new measurable

- **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.
- **irProgressive Disease (irPD):** Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

Impact of New Lesions on irRC New lesions in and by themselves do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD, which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- **Immune-Related Complete Response (irCR):** Complete disappearance of *all* tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
    - At least 25% increase in the sum of the products of all index lesions over nadir SPD calculated for the index lesions.
    - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.
- **Immune-Related Best Overall Response Using irRC (irBOR)** irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered. irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

Derivation of irRC overall responses

Measurable Response	Nonmeasurable Response		Overall Response
Index and new, measurable lesions (tumor burden),*%	Non-index lesions	New, non-Measurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal Progression	Any	irPR†
↓≥50	Any/Stable	Any	irPR†
↓≥50	Unequivocal Progression	Any	irPR†
↓<50 to <25↑	Any/Stable	Any	irSD
↓<50 to <25↑	Unequivocal Progression	Any	irSD
25	Any	Any	irPD†

*Decreases assessed relative to baseline (scan prior to start of any protocol therapy), including measurable lesions only
†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

7.3 Safety/Tolerability

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

8.0 ADVERSE EVENTS

8.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration through 30 days after the last [dose of study treatment. Any serious adverse event that occurs more than [30] days after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

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

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

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

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

8.2 Definitions

Adverse Event

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

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

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

Serious Adverse Event

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

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

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

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

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

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

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the

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

Expected Adverse Events

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

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

Unexpected Adverse Event

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

8.3 Adverse Event Characteristics

CTCAE Term

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

Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE *is clearly related* to the study treatment
Probable – The AE *is likely related* to the study treatment
Possible – The AE *may be related* to the study treatment
Unlikely – The AE *is doubtfully related* to the study treatment
Unrelated – The AE *is clearly NOT related* to the study treatment

8.4 Serious Adverse Event Reporting Guidelines

The Principal Investigator must be notified within 2 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related treatment.

The investigator must report all events meeting the criteria and definition of a serious adverse event that are unexpected and possibly related (definite, probable or possible) to study treatment within 7 business days of study team's knowledge if death or life threatening, and within 14 calendar days for all others. Events that meet the FDA reporting requirements will be reported to the FDA according to 21CFR312.32.if the study is conducted under an IND.

All Serious Adverse Events that are unexpected and possibly related (definite, probable or possible) to study treatment administration will be reported to the IRB using the OCTSU Serious Adverse Event form.

8.5 Routine Reporting

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

8.6 Reporting of Unanticipated Problems

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

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

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

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

9.0 DRUG INFORMATION

9.1 Pembrolizumab (Keytruda®)

- Other names for the drug: Keytruda®
- Description: Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial
- Classification: type of agent: Immunomodulatory; checkpoint inhibitor
- Mode of action: Pembrolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity.
- Pharmacokinetics: Based on a population analysis that included 2,841 patients in various dose range, the typical population clearance was 212 mL/day, volume of distribution at steady state was 6.1 L, and the terminal half-life was 23 days. The population PK analysis suggests steady state is obtained by 19 weeks with an every 3-week regimen and the systemic accumulation was 2.2-fold. The systemic accumulation in area under the curve (AUC), maximum concentration (Cmax) and trough concentration (Cmin) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.
- Side effects: Please see the package insert(s) for pembrolizumab. For the most recent safety update, please refer to the current package insert(s).
- Drug Interactions Please see the package insert for pembrolizumab for information regarding drug interactions.
- Contraindications: Please see the package insert for pembrolizumab for information regarding contraindications.
- Special Warnings and Precautions for Use: Please see the package insert(s) for pembrolizumab for information regarding special warnings and precautions for use.
- Storage and stability: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. This product does not contain a preservative. Administer immediately once prepared. If diluted pembrolizumab infusion solution is not used immediately, it can be stored either:
    - At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration for infusion.
    - Under refrigeration at 2°C–8°C (36°F–46°F) for no more than 24 hours. Do not freeze. Do not shake. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Preparation and Dispensing:
  Visually inspect drug product for particulate matter and discoloration prior to administration whenever solution and container permit. Pembrolizumab is a colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial. Prepare the solution for infusion as follows: Add 2.3 mL of Sterile Water to vial. Withdraw the required volume of pembrolizumab from the vial and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL. Discard partially used or empty

vials of pembrolizumab.

- Administration:
  Administer the initial infusion over 30 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not co-administer other drugs through the same intravenous line.

- Availability**:** Commercially available through Merck & Co., Inc. Standard of care in metastatic platinum refractory urothelial carcinoma.

10.0 CORRELATIVES/SPECIAL STUDIES

10.1 Sample Collection Guidelines

Tumor tissue should be identified prior to registration. An archived formalin-fixed paraffin embedded tissue block and/or fresh tissue will be submitted for each subject from prior cystectomy or biopsy of metastatic lesion (estimated tumor content >30% of nucleated cells in specimen). This tissue may be used for:

- PD-L1 testing of tumor cells and tumor infiltrating immune cells
- Next generation sequencing via MI-ONCOSEQ
- Tumor immune infiltrate sequencing via CIBERSORT

Plasma sample (5-10mL) at baseline only:

- 5-10 mL will be banked
- See below for collection and processing instructions

Serum samples (5-10 mL) at baseline only:

- For banking
- See below for collection and processing instructions

Serum collection and processing
Collect whole blood in a covered test tube. If commercially available tubes are to be used, the researcher should use the red topped tubes. These are available from Becton Dickinson (BD). BD's trade name for the blood handling tubes is Vacutainer. After collection of the whole blood, allow the blood to clot by leaving it undisturbed at room temperature. This usually takes 15-30 minutes. Remove the clot by centrifuging at 1,000-2,000 x g for 10 minutes in a refrigerated centrifuge.

The resulting supernatant is designated serum. Following centrifugation, it is important to immediately transfer the liquid component (serum) into a clean polypropylene tube using a Pasteur pipette. The samples should be maintained at 2-8°C while handling. The serum should be apportioned into 0.5 ml aliquots, stored, and transported at –20°C or lower. It is important to avoid freeze-thaw cycles because this is detrimental to many serum components. Samples which are hemolyzed, icteric or lipemic can invalidate tests.

Plasma samples collection and processing
Collect whole blood into commercially available anticoagulant-treated tubes e.g., EDTA-treated (lavender tops) or citrate-treated (light blue tops). Heparinized tubes (green tops) are not permitted. Cells are removed from plasma by centrifugation for 10 minutes at 1,000-2,000 x g using a refrigerated centrifuge. Centrifugation for 15 minutes at 2,000 x g depletes platelets in the plasma sample.

The resulting supernatant is designated plasma. Following centrifugation, it is important to immediately transfer the liquid component (plasma) into a clean polypropylene tube using a Pasteur pipette. The samples should be maintained at 2-8°C while handling. If the plasma is not analyzed immediately, the plasma should be apportioned into 0.5 ml

aliquots, stored, and transported at –20°C or lower. It is important to avoid freeze-thaw cycles. Samples which are hemolyzed, icteric, or lipemic can invalidate certain tests.

Tissue samples and banked serum/plasma should be delivered for analysis/storage to:

Attention: Javed Siddiqui, MS, MT (ASCP, CLsp (MB))
Michigan Center for Translational Pathology
[redacted]
Phone: [redacted]
Fax: [redacted]

10.2 Specimen Banking

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

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories [http://msa.med.umich.edu/policies/tissue-sample-collection-ownership-usage-disposition-within-all-umms-research-biorepositories].

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints, Sample Size and Accrual

The primary aim of this study is to determine the feasibility of treating patients with metastatic urothelial carcinoma who have progressed after platinum based chemotherapy with sequential pembrolizumab and SBRT. Treatment success will be defined as completion of 4 cycles of pembrolizumab and at least one course of treatment of SBRT within 15 weeks from first dose of pembrolizumab. The trial will define the combination treatment as feasible if 70% of the patients receive the treatment as defined. With 20 evaluable patients, if 14 out of 20 (70% [95% Confidence Interval: 50% - 90%]) achieve successful treatment then the trial will conclude that further evaluation of sequential pembrolizumab and SBRT should be explored. A patient is evaluable for feasibility and safety if they receive at least one dose of pembrolizumab. Patients who achieve a complete response prior to SBRT are not evaluable for feasibility. Non-evaluable patients will be replaced. With accrual of 1-2 patients per month the trial accrual is expected to take up to 24 months.

Secondary endpoints will include efficacy and safety. Efficacy will be measured using the following endpoints: best overall response by RECIST and Immune Related Response Criteria and progression-free survival by RECIST and Immune Related Response Criteria. Safety endpoints will measure the frequency and severity of grade 3-5 drug-related adverse events of the combination of SBRT and pembrolizumab.

Correlative plans are described separately below.

11.2 Data Analyses Plans

The primary analysis will report the count, proportion and corresponding 95% binomial confidence interval of evaluable patients who completed 4 cycles of pembrolizumab and at least one course of treatment of SBRT within 15 weeks from first dose of pembrolizumab.

The best overall response (CR + PR) by RECIST and Immune Related Response Criteria will be reported separately with counts, proportions and corresponding 95% binomial confidence intervals. Progression-free survival endpoints will be described with medians and Kaplan-Meier plots using product-limit estimates and associated 95% confidence intervals using RECIST and Immune Related Response Criteria separately. Frequency and severity of drug-related adverse events will be described. Each of the secondary endpoints will be described in the evaluable population and in the population who achieve treatment success as defined in the primary endpoint.

Correlative Analyses
PD-L1 expression on tumor cells and immune cells infiltrating tumor, and CIBERSORT/TIMER gene expression profiling correlatives will be analyzed with association to clinical outcomes using exact chi-square tests, t-tests, or Kaplan-Meier methods as is appropriate for each independent covariate and clinical outcome. Tumor mutational status and burden by tissue based next generation sequencing (MI-ONCOSEQ) results will be descriptive.

12.0 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan.

The study team will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Committee on a quarterly basis for independent review.

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