MSK Protocol Cover Sheet

A Safety Study of Avelumab plus SBRT in Malignant Mesothelioma (MPM)

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List of Abbreviations (alphabetical)	
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
CPK	Creatine phosphokinase
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4 DCE
DCE	Dynamic contrast-enhanced
DLT	Dose-limiting toxicity
DWI	Diffusion-weighted imaging
EOT	End of treatment
GGT	Gamma-glutamyl transferase
IRB	Institutional Review Board
irAE	Immune-related adverse event
KPS	Karnofsky Performance Status
mAb	Monoclonal antibody
MPM	Malignant pleural/peritoneal mesothelioma
MRI	Magnetic resonance imaging
ORR	Overall response rate
OS	Overall survival
PD	Progression of disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PR	Partial response
Q2W	Every other week
RECIST	Response Evaluation Criteria in Solid Tumors
SBRT	Stereotactic Body Radiotherapy
SD	Stable disease
SPD	Sum of the products of diameters
TB	Tuberculosis
TCRs	T-cell receptors
TILs	Tumor infiltrating lymphocytes
ULN	Upper limit of normal

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title	A Safety Study of Avelumab plus SBRT in Malignant Mesothelioma (MPM)
Investigational drug	Avelumab
Study Centers	MSKCC Main Campus and Regional Sites
Study Objectives	To evaluate the efficacy and safety (defined as the incidence of any grade 3+ non-hematologic toxicity) of combining SBRT and avelumab for the treatment of MPM
Study Endpoints	Primary Endpoint • Safety of avelumab + SBRT: rate of grade 3 or higher non- hematologic toxicity (CTCAE v4.0) Secondary Endpoint • • Overall response rate defined by modified RECIST 1.1 for mesothelioma • Response of irradiated (in-field) and unirradiated (out-of-field) lesions as defined by RECIST 1.1 • Progression-free and overall survival Exploratory Objectives • T-cell infiltration both in- and outside the irradiated field • Serum immune phenotype at baseline and after avelumab + SBRT • Concordance of imaging using diffusion-weighted and DCE-MRI, and PET with biopsy sample results
Patient Population	Patients with a histologically/cytologically proven malignant pleural or peritoneal mesothelioma who have received one or more lines of standard treatment.
Number of Patients	27 patients maximum 13 patients will be recruited for Stage 1. If requirements for expansion are met, another 14 patients will be recruited for Stage 2.
Inclusion Criteria (summarized)	1. Patient willing and able to provide written informed consent for the trial. 2. Patient age ≥ 18 at time of consent. 3. Unresectable or stage IV malignant pleural or peritoneal mesothelioma (MPM). 4. Histological and/or cytological confirmation of MPM. 5. At least one prior therapy 6. At least one targetable lesion appropriate for palliative SBRT. 7. Karnofsky Performance Score (KPS) ≥ 70% 8. Adequate organ function, defined below in Section 6.1

Exclusion Criteria (summarized)	1. Currently participating and receiving another study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment. 2. Continuous oxygen use 3. Known history of active TB (Tuberculosis), HIV, and/or Hepatitis B/C 4. Hypersensitivity to avelumab or any of its excipients 5. Prior monoclonal antibody treatment within 4 weeks prior to study Day 1 or has not recovered (i.e., ≥ Grade 1 at baseline) from adverse events due to agents administered > 4 weeks earlier. 6. Prior chemotherapy, targeted small molecule therapy, within 4 weeks prior to study Day 1 or has not recovered (i.e., ≥ Grade 1 at baseline) from adverse events due to a previously administered agent (excluding Grade 2 neuropathy). 7. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) within 4 weeks prior to study Day 1 or has not recovered (i.e., ≥ Grade 1 at baseline) from adverse events due to a previously administered agent
Study Drug	Avelumab; 10mg/kg delivered by IV infusion
Study Design	This clinical trial will be designed as a single-arm, single-institution safety study at Memorial Sloan Kettering Cancer Center Main Campus and Regional Sites. The main objective is to evaluate the safety of a novel combination of avelumab (anti-PD-L1 mAb) and stereotactic body radiation therapy (SBRT) for advanced malignant pleural and peritoneal mesothelioma (MPM). The treatment will consist of one dose of avelumab every other week as well as a short course of SBRT after the first two doses of avelumab. Avelumab will be continued up to 24 months or until disease progression. To further enhance our current understanding of tumor immunology as well as prognostic biomarkers, we will collect peripheral serum samples before, during and after treatment, and tumor biopsies of the irradiated and an unirradiated lesion (if available) before and after radiation. The safety endpoint of the trial will be assessed based on grade 3 or higher non-hematologic toxicity. We hypothesize that the combination of immunotherapy and SBRT will be safe and well tolerated. Furthermore, we believe that this combination therapy will lead to an increase in tumor-specific T-cells and neoantigen diversity along with a higher T-cell infiltration of irradiated and unirradiated tumor lesions and objective overall responses in lesions both in and outside the radiation field. Accrual is estimated to be 1 patient per month.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective of this study is to evaluate the safety of avelumab plus SBRT. This study is designed to include both pleural and peritoneal mesothelioma.
- The secondary objectives are to assess:
    - Overall response rate (ORR) using modified RECIST for mesothelioma treated with SBRT and avelumab.
    - Response of irradiated (in-field) and unirradiated (out-of-field) lesions defined by RECIST 1.1 for extrathoracic disease
    - Progression-free and overall survival
- Exploratory objectives are to evaluate T-cell infiltration and phenotype both in- and outside the irradiated field, serum immune phenotype before and after avelumab plus SBRT, and correlate imaging response (DW/DCE-MRI and PET) with biopsy sample results.

3.0 BACKGROUND AND RATIONALE

3.1 Malignant Mesothelioma

Malignant pleural/peritoneal mesothelioma (MPM) is a cancer commonly associated with prior asbestos exposure. The simian virus 40 (SV40) has also been discussed as a potential carcinogen [3, 4] as around 25% of MPM patients have no known asbestos exposure. Pleural mesothelioma, affecting the lining of the lungs, accounts for about 75- 80% of all cases while the peritoneal type, found in the abdomen, is present in 10-15% of mesothelioma patients. While the US incidence appears steady at 3,000 new diagnoses per year, the incidence of mesothelioma continues to increase globally and in some regions is epidemic.[5, 6] MPM is often unresectable at diagnosis and the mean overall survival is only 8-13 months.[7] MPM is almost universally lethal and therapeutic advances have largely plateaued over the past decade. Even with resectable disease, traditional treatments, including multimodality therapy, have a limited and transient impact on the disease. Local recurrences are quite common and cause tremendous morbidity for patients.[8] As there are no FDA-approved therapies for second-line treatment of MPM, an unmet need persists and the bar for therapeutic efficacy in this setting is low.

3.2 Clinical Data on Immunotherapy and Mesothelioma

The recent emergence of immunotherapy in cancer provides a new avenue for therapy in MPM. T-cell checkpoint inhibitors like anti-PD-1/anti-PD-L1 and anti-CTLA-4 have shown durable activity and prolonged disease stabilization in solid tumors like melanoma, NSCLC and colorectal cancer even after treatment cessation.[9, 10] Although anti-PD-1 treatment alone is currently being studied (clinicaltrials.gov NCT02399371) and has shown impressive preliminary results,[11] our proposal to combine PD-1 inhibition with radiation

therapy is a novel approach in MPM. There is already high-quality emerging evidence of activity of immunotherapy in MPM.

Kindler et al. reported on anti-CTLA-4 therapy as second- or third-line treatment of unresectable MPM at ASCO 2016. There was previous activity of tremelimumab shown in pre-treated MPM patients (Calabro et al., Lancet Oncology 2013). These were the results of the double-blind, placebo controlled DETERMINE study. Patients who progressed after 1 or 2 lines of prior therapy were randomized 2:1 to 10mg/kg q4 weeks for 7 doses, then q12 weeks to tremelimumab versus placebo. The primary endpoint was overall survival.
572 total patients were randomized, stratified by EORTC status, line of therapy, and anatomic site. There was no statistically significant difference in overall survival (median 7.7 vs 7.3 months, p=0.408).

Anti-PD-1/PD-L1 agents have shown some significant promise. At the 2015 AACR, Alley et al. presented the mesothelioma results of the KEYNOTE-028 trial, a non-randomized multi-cohort phase IB study of pembrolizumab for PD-L1 positive solid advanced tumors. In this cohort of 38 patients (out of 84 screened), each had $\geq$ 1% PD-L1 expression in tumor cells or PD-L1-positive stromal bands. The primary endpoint was safety, tolerability, and preliminary efficacy. 88% had received at least one line of prior therapy, most of which was a platinum-based agent in combination with pemetrexed. Treatment was pembrolizumab 10mg/kg every 2 weeks for up to 2 years, or until confirmed progression of disease. 60% of patients experienced a drug-related adverse event, although only 12% (3 patients) experienced grade 3 or higher toxicity. No patients discontinued therapy due to drug-related events. There was a 76% disease control rate, which was remarkable (24% overall response rate, with 52% stable disease). Given this significant response rate and potential for additional improvement, the role of immunotherapy, particularly with PD-L1 inhibitors is certainly warranted.

Data on safety and early efficacy information on avelumab in mesothelioma were first presented at the ASCO 2016 Annual Meeting by Hassan et al. 53 patients with unresectable pleural or peritoneal mesothelioma were recruited. These patients had progressed after a platinum-pemetrexed-containing regimen and were unselected for PD- L1 expression. They were treated with avelumab 10 mg/kg IV every 2 weeks until progression, unacceptable toxicity, or withdrawal. Tumors were assessed every 6 weeks (RECIST 1.1). Patients were followed for a median of 46 weeks. The overall response rate was 9.4% (5 partial responses; 95% CI: 3.1, 20.7) and an additional 4 were ongoing. Stable disease was observed in 25 patients (47.2%). This yielded a disease control rate of 56.6%. Median progression-free survival was 17.1 weeks (95% CI: 6.1, 30.1), and PFS rate at 24 weeks was 38.4% (95% CI: 23.3, 53.4). Grade ≥ 3 treatment-related adverse events occurred in 4 patients (7.5%). This included colitis, decreased lymphocytes, and increased GGT or CPK. There were no treatment-related deaths. These data indicate that avelumab has a reasonable toxicity profile and favorable activity in a PD-L1 unselected population. We note that this study was in an unselected cohort of patients.

Additionally, Calabro et al. are studying a combination of tremelimumab and durvalumab, an anti-PDL1 agent, in patients with MPM in the NIBIT-MESO-1 study, introduced at ASCO 2016.

3.3 Preclinical and Clinical Data on Radiation Therapy and Immunotherapy

Radiation therapy, in addition to being highly effective in local tumor control, has been observed to show anti-tumor effects in non-irradiated sites when combined with immunotherapy, first described in MSKCC"s department of radiation oncology.[12] The mechanisms of this so called "abscopal effect" have yet to be fully explained. Nevertheless, a growing body of evidence suggests that the effect can be attributed to antigen exposure by the cells killed by ionizing radiation, leading to an activation of the immune system through an enhanced repertoire of T-cell receptors (TCRs) in tumor infiltrating lymphocytes (TILs)[13, 14] and to an induction of proinflammatory cytokines.[15] Results from both preclinical and clinical trials highlight the potential synergy of radiation and immunotherapy. In a proof-of principle trial, 41 patients with solid tumors received chemoradiation for two sites of disease as well as GM-CSF (granulocyte-macrophage colony stimulating factor) injections. Of those patients, 26.8% (11) showed objective responses in a third, untreated lesion.[1] Interleukin-2 (IL-2)-based immunotherapy has been used as a treatment for melanoma and renal cancer for many years. Its historical response rate of 16% in melanoma has however been significantly improved to 71% (CI = 95%, 29-96%) by combining it with stereotactic body radiation therapy (SBRT).[16]

There are no results yet for clinical trials evaluating combined RT and anti PD-L1 therapy, but RT and anti-CTLA4 treatment has been tested in patients with melanoma and other cancers. Unirradiated lesions showed partial response and stable disease (each in 18% of patients) for a group of 22 melanoma patients treated with ipilimumab (CTLA-4 inhibitor) and RT to an index target.[14] Consequent mouse trials revealed that a partial immunity against RT and anti-CTLA-4 had developed after the treatment and that this phenomenon could be evaded by inhibiting PD-L1 or PD-1.[14] Survival in mice with GL261 gliomas was significantly higher after treatment with RT and anti-PD-1 compared to the control, RT only and anti-PD-1 only groups ($p<.001$, median survival 52, 26, 27 and 30 days respectively).[17] In a phase I/II study of patients with metastatic castrate-resistant prostate cancer, the combination of ipilimumab (anti-CTLA-4) and RT showed promising tumor response results and a manageable toxicity profile.[18]

3.4 Avelumab

Avelumab (initially known as MSB0010718C) is an investigational fully human anti-PD-L1 IgG1 monoclonal antibody. By inhibiting PD-L1 interactions, avelumab is thought to enable the activation of T-cells and the adaptive immune system. By retaining a native Fc-region, avelumab is thought to engage the innate immune system and may induce antibody-dependent cell-mediated cytotoxicity (ADCC).

Preclinical data are extensive in the potency of avelumab. Avelumab has the ability to lyse a range of human tumor cells in the presence of peripheral blood mononuclear cells (PBMC) or natural killer (NK) effectors. IFN-γ is able to enhance tumor cell PD-L1 expression and, in some cases, enhance ADCC tumor cell lysis. Purified NK cells are potent effectors for avelumab. Finally, similar levels of avelumab-mediated ADCC lysis of tumor cells are seen using purified NK as effectors from either healthy donors or cancer patients.[19]

Avelumab was found to have significant activity in a preclinical model of bladder cancer. MB49 murine tumor cells formed multifocal, superficial tumors on the mucosal wall of the bladder, similar to human transitional cell bladder tumors. Administration of avelumab resulted in antitumor effects and subsequently improved overall survival. Both were abrogated by selective in vivo depletion of CD4 or CD8 T cells. These findings suggest that in this murine bladder tumor model, interruption of the immune suppressive PD-1/PD- L1 complex using avelumab releases an adaptive immune response that significantly reduces tumor growth.[20]

Given the existing data on anti-solid tumor effectiveness of blocking P D 1/PD-L1 interaction, avelumab was rapidly translated into clinical trials under the JAVELIN clinical trial program. An umbrella study, JAVELIN Solid Tumor (Online, available https://clinicaltrials.gov/ct2/show/NCT01772004), sought to evaluate safety and efficacy of avelumab in metastatic and locally advanced solid malignancies.

3.5 SBRT

Stereotactic body radiotherapy (SBRT) represents a significant innovation in clinical radiation oncology. [21] SBRT allows the delivery of ablative radiation with relative sparing of high-dose to normal tissue. SBRT has been extensively studied in lung, pancreas, liver, and prostate cancers, and has also been used to ablate bone metastases. Local control exceeds 90% in spine and lung lesions. In palliation of previously irradiated or radioresistant bone metastases, SBRT can provide durable pain control. SBRT offers an excellent treatment for local management of metastatic or progressive lesions. SBRT is already offered in the routine management of early stage inoperable non-small cell lung cancers and associated with high local control and low t o x i c i t y .

MSKCC already has extensive experience treating MPM with radiation. Rimner et al. treated 67 patients with definitive or adjuvant pleural intensity-modulated radiation therapy.[8] Actuarial in-field failure rates at 1- and 2-years was 56% and 74% respectively. Distant failures occurred in 48% of patients. The predominant form of failure was local in- field failures, suggesting that dose-escalated radiation, as offered by SBRT, may improve local control without increasing dose-limiting lung toxicity. In addition, a significant number of patients had distant failures, suggesting there is a significant opportunity to improve systemic therapy.

3.6 Rationale for Study Design

In this context of promising preclinical and clinical results, compelling evidence supports our proposal to study treatment of stage IV malignant mesothelioma with combination anti- PD-L1 and SBRT. With this trial we will accomplish several things: 1) determine the overall response rate of combining checkpoint inhibition with radiation therapy with additional information on local control of both targeted and non-targeted disease; 2) confirm the safety of combined radiation therapy and anti-PD-L1 therapy; 3) determine the role of biomarkers to predict response to this type of therapy; and 4) expand our understanding of the mechanism of the abscopal effect. Since it is challenging to fully treat the diffuse pleural disease involved with MPM with local therapies, MPM is an excellent disease in which to study and answer these questions. If effective, this paradigm has the potential to transform the standard treatment of unresectable MPM. Furthermore, by examining a variety of biomarkers we will greatly expand the currently limited knowledge of predictive and influential biological factors in radiation and immunotherapy to support the optimization of individualized cancer care.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single-arm, two-stage study that will be conducted at Memorial Sloan Kettering Cancer Center Main Campus and regional sites. 13 patients will be accrued in the first stage and, if proven sufficiently safe, an additional 14 patients will be accrued in a second stage.

4.3 Intervention

The main objective is to evaluate the safety of a novel combination of avelumab (anti-PD-L1 mAb) and stereotactic body radiation therapy (SBRT) for end-stage malignant pleural and peritoneal mesothelioma (MPM).

The safety endpoint of the trial will be assessed based on grade 3 or higher non-hematologic toxicity.

One cycle of avelumab is defined as two weeks. The treatment will consist of one dose of avelumab every other week (Q2W) as well as a short course of SBRT after the first two doses of avelumab. Patients will receive avelumab 10mg/kg as an IV infusion every 2 weeks. Avelumab will be continued up to 24 months or until disease progression. Patients may continue Avelumab after RECIST-defined radiologic progression of disease if the following criteria are met: absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression]

requiring urgent alternative medical intervention; no significant, unacceptable or irreversible toxicities related to study treatment.

Patients will be treated with SBRT according to standard image-guided radiation treatment procedures. Patients will have a CT simulation (including 4DCT scanning if clinically indicated) with 2mm slice thickness and daily cone-beam CT verification of patient setup and tumor position. Patients will be treated in $\leq$ 8 fractions.

To further enhance our current understanding of tumor immunology as well as prognostic biomarkers, we will collect peripheral serum samples before, during and after treatment, and tumor biopsies.

4.4 Estimated Duration of Subject Participation

Subjects may be treated with avelumab for up to 24 months. All subjects will be followed for survival and assessed every 2 months as per Section 10 for up to 1 year following completion of avelumab or disease progression unless the Principal Investigator or Pfizer elects to end the study.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 SBRT

SBRT will be used to treat a designated lesion that is symptomatic or at risk of causing symptoms. SBRT will be performed with external beam ionizing radiation in accordance with institutional standard practice. 3D conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) will be used at the discretion of the treating radiation oncologist. Total SBRT dose will be between 30 and 60 Gy in $\leq$ 8 fractions as per standard of care.. The dose must satisfy institutional guidelines and minimize risk to adjacent organs at risk (see appendix 1 for reference).

5.3 Avelumab

Avelumab (also known as MSB0010718C) is a fully human anti-PD-L1 IgG1 monoclonal antibody. By inhibiting PD-L1 interactions, avelumab is thought to enable the activation of T-cells and the adaptive immune system. By retaining a native Fc-region, avelumab is thought to engage the innate immune system and may induce antibody-dependent cell-mediated cytotoxicity (ADCC). Avelumab has previously received Breakthrough Therapy Designation for Merkel cell carcinoma.

Avelumab will be provided by Pfizer. Avelumab will be stored, prepared, and administered as per MSKCC guidelines.

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

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

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1. Patient willing and able to provide written informed consent for the trial.

2. Patient age ≥ 18 at time of consent.

3. Histologically or cytologically confirmed malignant pleural or peritoneal mesothelioma (MPM).

4. No plans for surgical resection.

5. At least one prior line of systemic therapy. Note: Patients on prior immunotherapy are eligible.

6. At least one targetable lesion appropriate for palliative SBRT and one non-target lesion

7. Karnofsky Performance Score (KPS) ≥ 70%

8. If of childbearing potential, must be willing to use highly effective mode of contraception for at least one month prior, during, and for 2 months after the end of active therapy

9. Adequate organ function, defined as
   - Absolute Neutrophil Count ≥ 1.5K/mcL.
   - Platelet count ≥ 100K/mcL.
   - Adequate renal function as defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula or serum creatinine ≤ 1.5 x U L N
   - Hemoglobin ≥ 9g/dL (prior transfusion permitted)
   - Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range
   - AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver).

10. If the patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

6.3 Subject Exclusion Criteria

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

2. Prior radiation therapy precluding SBRT

3. Continuous oxygen use

4. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

5. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

6. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3)

7. Patient who rapidly progressed on prior immunotherapy, as determined by the treating physician, are not eligible.

8. Prior Therapies:
   a. Treatment with a monoclonal antibody within 4 weeks prior to study Day 1 or has not recovered (i.e., ≥ Grade 1 at baseline) from adverse events due to agents administered.
   b. Prior chemotherapy, targeted small molecule therapy, within 4 weeks prior to study Day 1 or has not recovered (i.e., ≥ Grade 1 at baseline) from adverse events due to a previously administered agent (excluding Grade 2 neuropathy).
   c. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) within 4 weeks prior to study Day 1 or has not recovered (i.e., ≥ Grade 1 at baseline) from adverse events.

9. Comorbidities or Prior Conditions:
   a. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

   b. Prior organ transplantation including allogenic stem-cell transplantation.

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

   d. Known history of active TB (Tuberculosis).

   e. Known history of HIV or known acquired immunodeficiency syndrome.

   f. Active Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection at screening or positive serologies indicating prior infection.

   g. Active infection requiring systemic therapy.

h. Evidence of interstitial lung disease or active, non-infectious pneumonitis.

i. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

10. Pregnant women or women who are breastfeeding or of childbearing potential and not using a highly effective method of birth control for at least one month prior to enrollment. If the risk of contraception exists, male and female subjects must use highly effective contraception throughout the study and for at least 60 days after last avelumab treatment.

    a. Highly effective contraception includes either 2 barrier methods (diaphragm, condom by the partner, copper intrauterine device, sponge, or spermicide), or 1 barrier method and 1 hormonal method (any oral, subcutaneous, intrauterine, or intramuscular registered and marketed contraceptive agent that contains an estrogen and/or a progesterone agent).

11. Vaccination within 4 weeks prior to the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines.

12. Concomitant use of the following medications

    a. Any investigational anticancer therapy.

    b. Any concurrent chemotherapy, immunotherapy, or biologic therapy. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

    c. Immunosuppressive medications including, but not limited to systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs, in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

13. Known contraindications to radiotherapy

7.0 RECRUITMENT PLAN

Eligible patients with malignant pleural or peritoneal mesothelioma will be recruited from the Thoracic Medical Oncology and Radiation Oncology departments at MSKCC. An attending physician of the Thoracic Medical Oncology and Radiation Oncology department will evaluate all patients. Participation is voluntary. The consenting physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits and experimental nature of this treatment program.

Memorial Hospital is a major referral center for MPM. In addition, the study information may be placed on the institutional hospital website to maximize recruitment.

Patients under the age of 18 are excluded because this disease does not occur in patients that age, and the safety of these treatments has not been established for them. The

patient population includes all patients under the care of attending surgical, medical and radiation oncologists at MSKCC main campus or regional sites. Every attempt will be made to recruit women and minorities to participate in this study. There are no genders or racial restrictions.

8.1 PRETREATMENT EVALUATION

To be completed within 45 days prior to starting avelumab unless otherwise specified:

1. Signed informed consent for study participation
2. FDG-PET scan
3. CT of the chest, abdomen, and pelvis, preferably with contrast. The companion CT scan from the above FDG-PET scan may fulfill this requirement.
4. MRI of the lesion to be irradiated according to the following guidelines in the MSKCC Department of Radiation Oncology
    a. Contraindication to MRI (i.e. pacemaker) = no participation in MRI component.
    b. Contraindication to contrast only = MRI w/o contrast
    c. No contraindication = MRI with contrast
5. 12-lead Electrocardiogram (EKG)
6. History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (Karnofsky)
7. Serum or urine pregnancy test for all women of childbearing potential (serum pregnancy test within 14 days or urine pregnancy test within 24 hours of starting avelumab)
8. CBC with differential and platelet count, CMP (including Na, Cl, BUN, Creatinine, K, CO2, glucose, AST, ALT, alkaline phosphatase, total bilirubin, calcium, albumin, and total protein)
9. Free T4 and TSH
10. Serology for HEP BsAg, HBcAb and hepatitis C antibody within 30 days prior to starting avelumab
11. Baseline blood test for research purposes (See Section 10.4)
12. Tumor biopsy for confirmation of either progressive or metastatic disease completed as standard of care of two lesions, a lesion to be irradiated and a lesion to be un-irradiated. Biopsy to be core needle biopsy up to 4 cores, 1 core to be sent to pathology and 3 cores to be sent to lab for research for each site, preferably 18-gauge or larger, specified prior to biopsy, permanently fixed, managed by CSP, Correlative Science Program.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Dosing Instructions and Schedule

9.1.1 Avelumab Dosing Instructions and Schedule

One cycle of avelumab is defined as two weeks. Administration of avelumab will commence after completion of pre-treatment procedures. Patients will receive avelumab 10mg/kg as an IV infusion Q2W. In order to mitigate infusion related reactions, a premedication with an antihistamine and with acetaminophen 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500- 650 mg acetaminophen IV or oral). The treating oncologist may use equivalent or similar medications as available at their discretion.

Two cycles will be given before starting radiation therapy. After 2 cycles of avelumab, a short course of SBRT (after the end of Cycle 2 and before Cycle 3, Day 1) will be delivered to a portion of MPM that is symptomatic or at risk of causing symptoms. Avelumab treatment continues during and after RT for up to two years or until disease progression. Avelumab may be continued after disease progression at the discretion of the investigator if criteria in section 4.2 are met.

The first day of dosing is considered Day 1 of the cycle. Day 1 of Cycle 1 is considered the date of first dose and is used to determine the maximum 24 months of treatment. Trial treatment should be administered on Day 1 of each cycle. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis.

9.1.2 SBRT Dosing Instructions and Schedule

SBRT will be administered after 2 cycles of avelumab are complete, with fractionation and schedule at the discretion of the treating radiation oncologist. The radiation dose and organ dose constraints will be in accordance with standard institutional guidelines (see appendix 1). Avelumab and SBRT should not be delivered on the same day. SBRT may be delayed up to 6 weeks for immunotherapy toxicity management. If the patient is unable to receive radiation within the 6 weeks, they will be removed from protocol and replaced.

Patients will be treated on an outpatient basis. Patients will be evaluated by the radiation oncology team and then undergo simulation for 3D-CRT, IMRT, or VMAT, the choice of which is determined by the radiation oncologist.

Each patient will be positioned in a custom immobilization and undergo a CT scan (slice spacing 2-2.5 mm, depending on the scanner) for treatment planning.

The radiation oncologist will delineate the gross tumor volume (GTV) on the planning scan. If clinically indicated for lesions within the chest, only, the 4D-CT scan will be used to account for respiratory motion.

Target volumes: The definitions of volumes will be in accordance with the 1999 ICRU report #62.

Definition of the gross tumor volume (GTV):
The volume determined to clinically correspond with the area require ing palliation will constitute the GTV.

Definition of the internal target volume (ITV):
For patients who undergo 4DCT simulation, only: an ITV will be created based on the 4D-CT scan to account for all respiratory motion throughout the respiratory cycle, thus resulting in a motion-inclusive ITV.

Definition of the clinical target volume (CTV):
The CTV will be defined as the ITV plus typically 0.2cm to account for microscopic tumor extension.

Definition of the planning target volume (PTV):
The PTV will include the CTV plus a margin of 0.5 cm to account for setup uncertainties.

Critical normal tissues in proximity to the irradiated lesion will be contoured. Hypofractionated guidelines based on current MSKCC guidelines will be applied (see appendix 1).

Isocenter is at the center of the GTV. Treatment is delivered with 6 or 15 MV photon beams. IMRT/VMAT will use the dynamic multileaf collimator (DMLC or sliding window) technique, on a Varian LINAC. The IMRT optimization algorithm uses an iterative gradient search method to minimize a quadratic objective function that can include terms to impose target dose uniformity, limit normal tissue maximum and mean doses and impose dose-volume constraints. Calculations are performed on a commercial treatment planning system using the analytic anisotropic algorithm (AAA) or Acuros algorithm (Varian Eclipse™).

Radiation will be given outpatient Monday to Friday, excluding holidays, until all ($\leq$ 8) treatments have been completed. If the patient misses a scheduled treatment, this treatment will be added on the end of the initial treatment plan. Each treatment day, the patient will be positioned supine on the treatment table with custom immobilization. Patients are first positioned with the use of skin tattoos and an in-room laser localization system. Patients will then undergo a cone-beam CT prior to each fraction. Refinements in patient positioning are made based on the on-board 3D imaging. Patients will be matched based on the tumor within a 2mm tolerance, which will be approved by the attending radiation oncologist. The radiation treatment will then be administered. All patients will be monitored for gross body movement using intra-fraction motion such as infrared, Align RT or interval KV bone match.

9.2 Monitoring of Dose Administration

Subjects will be monitored during avelumab administration and for a minimum of 2 hours after infusion with assessment of vital signs. Subjects will be monitored during avelumab administration and for a minimum of 30 minutes after infusion with assessment of vital signs if there are no infusion related reactions within the first 8 cycles. As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and s t u d y personnel m u s t be trained to recognize and treat anaphylaxis. The study site must have immediate access to

emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents at the treating oncologist's discretion, and oxygen should be available for immediate access.

9.3 Concomitant Medications

9.3.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 9.3.2.

9.3.2 Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The Principal Investigator must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy.
- Any concurrent chemotherapy, immunotherapy, or biologic therapy. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- Immunosuppressive medications including, but not limited to systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs, in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

9.4 Dose Modification and Discontinuation

9.4.1 Adverse Drug Reactions (ADRs) Requiring Avelumab Discontinuation or Dose Modification

Any Grade 4 ADRs require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with avelumab (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab will be permanently discontinued.

9.4.2 Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the study drug infusion rate by 50% and monitor closelyfor any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptlyto symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	Stop study drug infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closelyfor any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the study drug infusion immediatelyand disconnect infusion tubing from the subject. Subjects have to be withdrawn immediatelyfrom study drug treatment and must not receive any further study drug treatment.
- Once the avelumab infusion rate has been decreased by50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. - If hypersensitivityreaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common TerminologyCriteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatorydrugs.

Additional Modifications for Patients with Grade 2 Avelumab Infusion-Related Reactions: In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Section 9.4.2 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. Atthe next cycle, the investigator may consider the addition of H2-blocker antihistamines (e.g., famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedications. Prophylactic steroids are NOT permitted.

Management of Avelumab-related Severe Hypersensitivity Reactions and Flu-like Symptoms: Many mAb therapies can induce flu-like symptoms and hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment if required. Patients should be placed on monitors immediately and epinephrine injections and dexamethasone infusions should be available for immediate access.

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable nonsteroidal anti-inflammatory drugs (NSAID) dose (e.g., ibuprofen 600 mg, naproxen sodium 500 mg)

may be administered at the investigator's discretion 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (e.g., paracetamol or ibuprofen) and rigors (e.g., meperidine) may be given to patients at the discretion of the investigator.

9.5 Management of Avelumab Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainlydependent upon severity (NCI-CTC AE grade):

Grade 1 to 2: treat symptomaticallyor with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

Treatment of gastrointestinal, dermatological, pulmonary, hepatic and endocrine irAEs should follow guidelines set forth in the table below.

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/dayover Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapyper protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4

Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological ir AEs		
Grade of Rash (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatologyconsult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delayof avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonaryand Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonaryand Infectious Disease consults Monitor symptoms daily, consider hospitalization	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume

	1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonaryand Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin >ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy Increase frequencyof monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue avelumab therapy Increase frequencyof monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

	if clinicallywarranted	
Endocrine ir AEs		
Endocrine Disorder	**Management**	**Follow-up**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinologyconsult if needed Start thyroid hormone replacement therapy(for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinologyconsult Start thyroid hormone replacement therapy(for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Hypopituitarism/Hypophysitis (secondaryendocrinopathies)	If secondarythyroid and/or adrenal insufficiencyis confirmed (i.e. subnormal serum FT4 with inappropriatelylow TSH and/or low serum cortisol with inappropriatelylow ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressiv e therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	
Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. BNP, troponin, CK-MB) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize. In the presence of life threatening cardiac decompensation consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following

	etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as appropriate per cardiology consult. * Consider myocardial biopsy if recommended per cardiology consult.	cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate per cardiology consult. * Methylprednisolone 1-2 mg/kg/day. Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressions (e.g. azathioprine, cyclosporine A).
*Local guidelines, or e.g. ESC guidelines (https://www.escardio.org/Guidelines/Clinical - Practice-Guidelines) or AHA guidelines (http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001)		
Renal ir AEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.

Grade 4 Creatinine increased > 6 x ULN	Permanentlydiscontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrologyconsult	f returns to Grade ≤1: Taper steroids over at least 1 month.
Other irAEs (not described above)		
Grade of other ir AEs (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanentlydiscontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanentlydiscontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanentlydiscontinue avelumab therapy Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common TerminologyCriteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

9.6 Management of Radiation Side Effects

Toxicities related to SBRT will be managed according to institutional supportive care guidelines.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

A calendar is presented below. Further explanation of each visit is provided after the table.

Study Calendar

Visit	Screening 1	2	3	4	5	6	7	8	9	10	11-EOT	End of Treatment Visit[6]
Treatment		C1	C2	SBRT[5]	C3/2 Wks Post - SBRT	C4	C5	C6	C7	C8/2M Post-SBRT	C9 to EOT	
Days (approx.)	-45	1	15	29	43	57	71	85	99	113		
Week of Treatment		1	3	5	7	9	11	13	15	17	19 – EOT	30 days and 90 days after last Avelumab
Visit Window	-45 days		+/- 3 days	+/- 7 days	+/- 7 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 7 days	+/- 3 days	+/- 14 days
Informed Consent, Demographics	X											
Medical History, Physical Examination[1]	X	X	X		X	X	X	X	X	X	X (Every Cycle)	X
Recording of Adverse Events		X	X		X	X	X	X	X	X	X (Every Cycle)	X
FDG-PET Scan	X				X (Prior to biopsy)							
CT chest, abdomen, pelvis[2]	X				X					X	X (q2 months post SBRT into follow-up period)	
DW/DCE – MR (unless contraindicated)	X				X (Prior to biopsy)							
12-lead EKG	X											
Serum or urine pregnancy test[3]	X											X
CBC, CMP	X	X	X		X	X	X	X	X	X	X	X
Free T4/TSH	X					X				X	X[8]	X
Serology[4]	X											
Research Blood Tests	X		X		X					X		
Tumor Biopsies	X[9]				X							

[1] Including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (Karnofsky).

[2] Preferably with contrast. The companion CT scan from the FDG-PET scan may fulfill this requirement.

[3] For all women of childbearing potential (serum pregnancy test within two weeks or urine pregnancy test within 24 hours of starting avelumab)

[4] HepBsAg, HepBcAb and hepatitis C antibody (negative test acceptable prior to screening period) within 30 days prior to starting avelumab.

[5] Patient simulated for radiation treatment no later than 20 days after Cycle 1, Day 1.

[6] 90 Day Short-term Follow-up Visit can be conducted over the phone by a RN, NP, or MD. If any concern arises, the patient will be called in for a follow-up visit within 5 calendar days for appropriate assessments (as per the investigator's medical judgment).

[7] The research blood test should occur within 3 days prior to Avelumab Administration.

[8] Free T4/TSH will be performed at cycle 12 and every 4 cycles until EOT.

[9] Standard of Care biopsy, for irradiated lesion and non-irradiated lesion. Biopsy will collect 4 cores, 1 core will be treated with formalin, will be sent to pathology and the remaining 3 cores will be fresh frozen and sent for research, per lesion.

10.2 Pre-Treatment

As Per Section 8.0

10.3 At Every Cycle (+/- 3 days)

1. History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (Karnofsky)
2. Report side effects
3. CBC with differential and platelet count, CMP (including Na, Cl, BUN, Creatinine, K, CO2, glucose, AST, ALT, alkaline phosphatase, total bilirubin, calcium, albumin, and total protein)
4. Treatment with avelumab
5. Free T4/TSH (every 4 cycles)

10.4 Two weeks after Irradiation (+/- 7 days)

1. Repeat biopsy of initially biopsied irradiated lesion and the unirradiated lesion (biopsy to be core needle biopsy up to 4 cores, preferably 18-gauge or larger, specified prior to biopsy, permanently fixed, managed by CSP Correlative Science Program)
2. FDG-PET scan (must be completed prior to biopsy)
3. DW/DCE-MRI with contrast of the lesion to irradiated (must be completed prior to biopsy) as described in Section 8.0 to be completed in the MSKCC Department of Radiation Oncology.

4. Research blood tests

10.5 Research Blood Tests

Baseline, at cycle 2s of avelumab, at cycle 3, and 2 months after completing irradiation. Specimens should be collected prior to drug administration. Four (4) tubes of blood are to be collected in BD Vacutainer® CPT™ Cell Preparation Tubes with Sodium Heparin. Each tube should contain approximately 10 cc of blood. Tubes will be processed as follows:

1) Tubes will be inverted several times immediately after collection. For serum tubes, blood will be allowed to clot for 30 minutes in a tube rack
2) Adhesive labels identifying patient ID, MRN, and date of collection must be attached to each tube
3) Time and date will be completed on the requisition form
4) All collected tubes and forms are placed in a biohazard Ziplock bag at room temperature with protective padding
5) Specimens are sent and processing will be performed according to institutional practice in the Immune Monitoring Facility (IMF).

10.6 Serial Imaging

CT of the chest, abdomen, and pelvis, preferably with contrast, will be performed every 2 months after completing SBRT (+/- 14 days) through the follow-up period.

10.7 End of treatment visits at 30 and 90 days after last avelumab (+/-14 days)

1. History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (Karnofsky)
2. Report side effects
3. CBC with differential and platelet count, CMP (including Na, Cl, BUN, Creatinine, K, CO2, glucose, AST, ALT, alkaline phosphatase, total bilirubin, calcium, albumin, and total protein)
4. Serum or urine pregnancy test for women of childbearing potential
5. Free T4/TSH

10.8 Followup Period Visits (every 2 months +/- 14 days)

Patients will be seen and evaluated by a physician every 2 months during the follow-up period. They will undergo standard of care serial imaging as per Section 10.5, blood work (CBC, CMP, Free T4/TSH), and a history and physical examination.

11.1 TOXICITIES/SIDE EFFECTS

Expected toxicities from SBRT are highly dependent on location of the radiated lesion. Some of these toxicities may include fatigue, dermatitis, pneumonitis, esophagitis, chest wall pain, nausea, vomiting. In very rare cases, patients may experience brachial plexopathy, myelitis, bronchial damage, vascular damage, pericarditis, and/or hepatitis.

Primary toxicities of concern include radiation pneumonitis. Grade 2 and 3 pulmonary toxicity may be observed in 10% and 3% of patients, respectively. Other grade 2 –4 toxicities included chest wall pain in 20%, fatigue in 15-20%, esophagitis in 5-10%, and skin toxicity in 5-10% of patients. Inferior thoracic lesions may have an increased risk of liver, bowel, and kidney injury.

Possible short and long-term toxicities from avelumab include thyroid dysfunction requiring thyroid hormone replacement, adrenal crisis, liver function test abnormalities, pneumonitis, rash, diarrhea, and colitis. In a Phase 1b study of avelumab in patients with mesothelioma, treatment-related adverse events occurred in 41 of 53 patients (77.4%). The most common (>10%) were infusion-related reactions (20 [37.7%]), fatigue (8 [15.1%]), chills (8 [15.1%]), and pyrexia (6 [11.3%]), all of which were grades 1/2. Grade ≥ 3 treatment- related adverse events occurred in 4 patients (7.5%). This included colitis, decreased lymphocytes, and increased GGT or CPK. There were no treatment-related deaths.

11.2 Safety Monitoring

Subjects will be evaluated for occurrence of AEs at each visit. Events will be characterized and reported as described below. Safety will also be monitored by performing physical exams and routine laboratory procedures.

Extended safety follow-up:

- Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration.
- The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

These visits are included in section 10.0

11.1.1 Adverse Events and Serious Adverse Events

Definitions of AEs, non-serious AEs, and serious adverse events (SAEs), as well as reporting guidelines are provided below.

Definition of Adverse Event and Non-Serious Adverse Event

The following definition of AE will be used for the study: "any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to medicinal (investigational) product." This definition includes any abnormalities or anomalies that were not seen at baseline or which worsened during the course of the study, if present at baseline.

A "non-serious" adverse event is any event that does not meet the definition of "serious adverse event" as presented, below.

Reporting and Treating Non-Serious Events

It is the responsibility of the investigator to perform regular assessments for AEs. Subjects will be regularly queried about the occurrence of any AEs and will be monitored throughout the study for reactions to study drug and/or study procedures. The investigator and clinical staff will record all AEs, whether volunteered by or elicited from the subject, at any time during a subject's participation in the study. Abnormal laboratory findings (e.g., hematology, comprehensive metabolic panel) or other abnormal assessments (e.g., vital signs) will be recorded as AEs if they are judged as clinically significant by the investigator.

All subjects experiencing an AE will be evaluated by the investigator and monitored until resolution of the events or until the investigator deems the event clinically stable and/or at an acceptable level. Unless the event requires hospitalization (SAE), medical treatment will be provided to the subjects at the unit and treatment medication and/or medical procedures will be provided per the treating-investigator "s clinical discretion. All clinically significant AEs, including clinically significant laboratory abnormalities, will be followed until resolution. AEs meeting the definition of SAEs require special reporting in addition to documentation in the CRDB as described below.

All AEs, including clinically significant laboratory and assessment abnormalities will be recorded according to "Common Terminology Criteria for Adverse Events" V4.0 (CTCAE) and must be recorded in the CRDB. Events occurring prior to initiation of first dose should be recorded on the Medical History page of the CRDB. Any AE occurring after initiation of first dose of study drug should be recorded on the Adverse Event page of the CRDB. AEs should be recorded in the CRDB using the medical terminology found in the source documentation. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology.

It is the investigator's responsibility to provide his/her assessment of the relationship of the event to the study drug and the severity of the event using the following scales:

- Relationship

- Unrelated: The AE is clearly attributable to a concurrent illness, concurrent medication, clinical state, or environmental factor other than the investigative agent.
- Unlikely: The occurrence of the AE does not follow the study in a temporal sequence and/or based upon available subject information, e.g., medical history, disease process, known pharmacology of drug, a relationship between the drug and AE is unlikely.
- Possible: The AE follows a reasonable temporal sequence from the time of study drug administration, but it is possible that other factors; e.g., subject's clinical state or concomitant mediations, environmental factors, or the drug's pharmacology, may have caused the AE .
- Probable: The AE follows a reasonable temporal sequence from the time of study drug administration, follows a known response pattern of the medication class, and cannot be reasonably explained by other factors.
- Definite: The AE follows a reasonable temporal sequence from the time of study drug administration, follows a known response pattern of the medication class, is a commonly associated AE, and is certainly explained by the study intervention.

- Severity

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V4.0. For those adverse events not listed in the CTCAE, the following grading system should be employed:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable
- Life-threatening (CTCAE Grade 4): Life-threatening or disabling AE
- Death (CTCAE Grade 5): Death-related AE.

Definition of Serious Adverse Event

The following definition of SAE applies for the study: "a serious AE means any AE occurring at any dose that results in any of the following outcomes: death, a life- threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or overdose of study drug. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the subject, or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is any AE that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (e.g., it does not include a reaction

that, had it occurred in a more severe form, might have caused death)." Refer to section 17.2 for "Reporting and Treating Serious Adverse Events."

Pregnancies

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 5 calendar days to the MSKCC Safety Office and within 2 working days to Pfizer Safety (Pfizer U.S. Clinical Trial Department, Fax 1-866-997-8322, OR USA.AEReporting@pfizer.com specifying Protocol, Subject, Site/PI, and SAE/Onset).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For the purposes of this study, patients will be evaluated for response every 2 months after completing SBRT (approximately 8 weeks, or every 4 cycles). Modified RECIST for mesothelioma and RECIST 1.1 criteria will be used [22]. CT scan of the chest, abdomen, and pelvis will be used for response assessment. The companion CT from an integrated PET/CT examination is suitable for this requirement. As part of the secondary endpoints, progression-free and overall survival will be recorded. Progression-free survival is defined as the length of time from the start of active treatment (avelumab) until removal from study due to progressive disease (defined by modified RECIST 1.1) or death. Removal from study due to toxicity will be counted as censoring. Overall survival is defined as the length of time from the start of active treatment until death.

Modified RECIST for Mesothelioma [23, 24]

The modified RECIST criteria for mesothelioma use unidimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum. In our protocol, the irradiated lesion is not required to be intrathoracic. This is measured on CT scan in 2 sites at 3 different levels at least 1cm apart. At reassessment, the thickness must be measured at the same position and level. Exhaustive documentation of non-measurable lesions are not required. The sum of tumor diameters is used to measure response.

Definitions of Overall Response	
Complete Response (CR)	Disappearance of all target lesions who no evidence of tumor elsewhere.

Partial Response (PR) Stable Disease (SD)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Response neither meeting the criteria of CR, PR or PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of tumor measurements over the nadir measurement, or appearance of one or more new lesions.

RECIST 1.1

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of non-target lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
Progressive Disease (PD)	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

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

PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NE = inevaluable

13.1 CRITERIA FOR REMOVAL FROM STUDY

Patients should **permanently** discontinue treatment with avelumab for the reasons enumerated in Section 9 or in the event of:

- Intolerable adverse events (e.g. CTCAE v4.0 grade 3 or 4) that cannot be managed by dose modification or delay
- Further dose modification or delay considered necessary but not allowed per protocol section 9.4
- Pregnancy[1]
- Withdrawal of informed consent[2]
- If the treating physician determines that it is in the best interest of the patient to stop study drug
- Non-compliance with the defined treatment plan

Patients will be removed from study after treatment ends in the event of:

- Death
- Pregnancy[1]
- Withdrawal of informed consent[2]
- Non-compliance with the defined follow up studies

[1]**Pregnancy:** In case of a patient or the patient's partner becoming pregnant during the trial the investigational drug has to be immediately stopped and the patients must be followed-up until birth or other termination of the pregnancy. Repeat counseling on birth defect risk must be offered.

[2]**Consent withdrawal:** in case a patient withdraws his/her consent for taking drug, it is of utmost importance for the robustness and integrity of the trial results that his/her safety data are recorded until the end of the 52 weeks period. Thus, all patients will be asked to follow their visit schedule until 52 weeks.

Patients who discontinue from this trial are not allowed to be reenrolled in this trial. Patients who discontinue medication within the first two weeks (during the washout period) will be replaced. For the patients who stopped trial before enrollment, their data will be part of the description of the screening population.

14.0 BIOSTATISTICS

The primary endpoint, the safety of a combination of avelumab and SBRT, will be defined based on the rate of any grade 3 or higher non-hematologic toxicity within the first 3 months after SBRT (for the rest of the section this will be referred to as AE). A two-stage stopping rule will be used to protect patients" safety. If 3 or more among the first 13 patients develop AEs, then the trial will be stopped and declared unsafe. Otherwise, an additional 14 patients will be enrolled and treated. If, among the total 27 patients, 5 or more patients are observed to have AEs, then the trial will also be declared unsafe. This stopping rule has a power of 80% declaring the true AE rate of 0.1 or lower safe, and a type 1 error rate (alpha) of 5% declaring true AE rate of 0.3 or higher safe.

For secondary endpoints, the overall response and the irradiated lesion and non-irradiated lesion response rates (4 months from start date of the combined therapy) based on RECIST 1.1 response criteria will be summarized by sample proportions and their confidence intervals. PFS and OS will be evaluated by Kaplan-Meier method.

For the exploratory objectives, we will evaluate changes of T-cell infiltration and serum immunophenotype at baseline and after SBRT + immunotherapy both in- and outside the irradiated field. The former is measured as numerical values so we will use Wilcoxon signed-rank test. The latter is categorical so we will tabulate it and employ the marginal homogeneity test. Due to the expected small sample size, results will be interpreted cautiously. The imaging studies using DWI-MRI and DCE-MRI, and FDG-PET will be correlated with biopsy results by McNemar's tests.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed.

All participants must be registered through the Clinical Trials Management System (CTMS) at Memorial Sloan-Kettering Cancer Center. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist and other relevant documents must be uploaded to CTMS. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

Not applicable in this study.

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secured database (Medidata Rave) at Memorial Sloan-Kettering Cancer Center. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of two times per year, or more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data safety and quality. At a departmental/PI level, there exist procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA, and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Deputy Physician-in-Chief of Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

· MSK Investigator-Initiated Trials (IITs; MSK as sponsor)

· External studies where MSK is the data coordinating center

· Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant, or by the end of the year one if no accruals, and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.1 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Memorial Sloan-Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described.

Exclusion of Lactating or Pregnant Women: Lactating and pregnant women are also excluded because of unknown effects of immunotherapy on a developing fetus or nursing infant.

Children have been excluded from this study as mesothelioma is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established.

Benefits: It is possible that this treatment will result in shrinkage of mesothelioma or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including, CT scans, all drug administration fees and all hospitalizations, as well as for complications of treatment. Avelumab will be supplied to patients by Pfizer at no cost. Patients will not be responsible for the costs of blood procurement obtained for research purposes, the cost of special testing of any tissue for research purposes, or the cost for obtaining the tumor biopsy for research purposes.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: Patients may be eligible for other investigational studies or focus on palliative care options.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients" records and pathology slides, as required.

17.2 Privacy

MSK"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research

Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized, de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information, which will not include protected health information such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- List any additional events that require SAE reporting (pregnancy, AEs of special interest (AESI), secondary malignancies, etc.)

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30 days after the participant's last investigational treatment/intervention. Any event that occurs after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (e.g., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP Office per IRB SOP RR-408 'Reporting of Serious Adverse Events,' the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)

- If the AE was expected
- Detailed text that includes the following
  - An explanation of how the AE was handled
  - A description of the participant's condition
  - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

For multicenter trials where MSK is the data coordinating center, please refer to the MSK Multicenter Trial Addendum. All required SAE reporting to the funders and/or drug suppliers will be completed by MSK only.

17.3.1 SAE Reporting to Study Sponsor / Drug Supplier

The following reportable events must be submitted to Pfizer within 24 hours (or immediately for death or life-threatening events) using the provided *Investigator-Initiated Research Serious Adverse Event Form (IIR SAE)* with *the Pfizer Reportable Events Fax Cover Sheet* with each SAE submission.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy"s Law cases): These events are considered important medical events and should be reported as SAEs.

Detailed guidance on the safety reporting is provided in the *Safety Reporting Reference Manual.*

Contact information for submission of reportable events to Pfizer:

- Fax: Pfizer U.S. Clinical Trial Department, Fax 1-866-997-8322.
  or
- E-mail: USA.AEReporting@pfizer.com, specifying:
  - PROTOCOL:
  - SUBJECT:
  - SITE/PI:
  - SAE/ONSET:

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Both the participant and the consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1: SBRT Organs at Risk Dose Constraints