DF/HCC Protocol #: 18-464

TITLE: A Phase 2 Study of Avelumab in Combination with Bladder-Directed Radiation in Cisplatin-Ineligible Patients with Muscle-Invasive Urothelial Carcinoma of the Bladder

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EMD Serono to supply:

Study drug, Avelumab (EMD Serono), as well as funding for this study.

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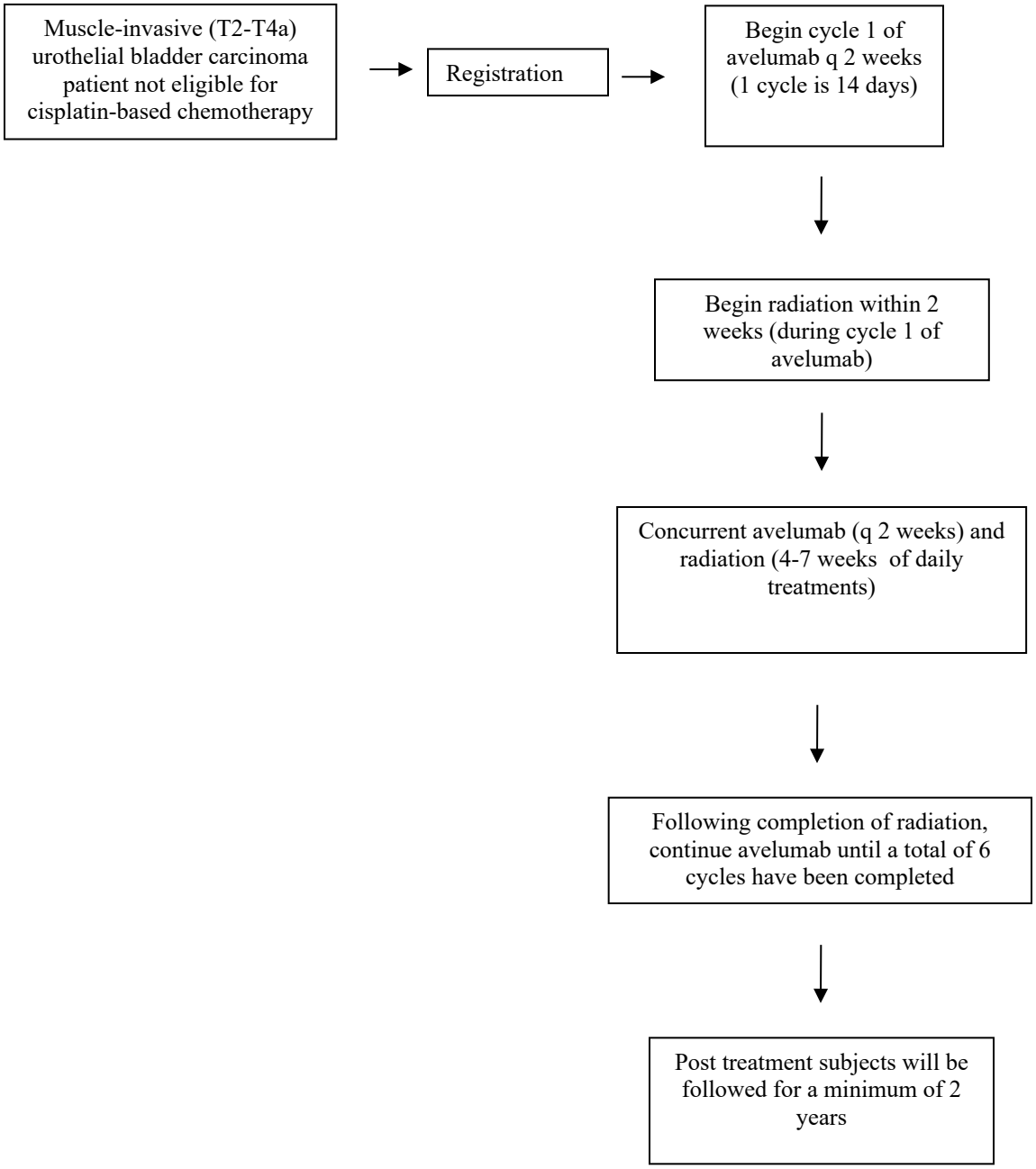
SCHEMA


Muscle-invasive (T2-T4a) urothelial bladder carcinoma patient not eligible for cisplatin-based chemotherapy
Registration
Begin cycle 1 of avelumab q 2 weeks (1 cycle is 14 days)
Begin radiation within 2 weeks (during cycle 1 of avelumab)
Concurrent avelumab (q 2 weeks) and radiation (4-7 weeks of daily treatments)
Following completion of radiation, continue avelumab until a total of 6 cycles have been completed
Post treatment subjects will be followed for a minimum of 2 years

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1. OBJECTIVES

1.1 Study Design

This study will investigate the safety and efficacy of the combination of the anti-PD-L1 agent avelumab and bladder-directed radiation in patients with muscle-invasive urothelial carcinoma of the bladder.

1.2 Primary Objective

To assess efficacy of the combination of avelumab and radiation in cisplatin-ineligible muscle-invasive bladder patients as measured by the complete clinical response rate at 3 months following completion of radiation.

1.3 Secondary Objectives

1. To assess locoregional control, progression-free survival, and overall survival
2. To assess patient-reported quality-of-life using QLQ-C30 and FACT-Bladder instruments at the following timepoints: baseline, end of radiation, and at each follow-up visit
3. To explore the association of tumor PD-L1 expression, immune cell subsets, T cell receptor diversity, mutational status, immune-related gene expression signatures, circulating immune cell subsets, and plasma/urine cell-free DNA with treatment response

2. BACKGROUND

2.1 Study Disease

Nearly 70,000 new cases of urothelial bladder cancer are diagnosed each year in the US.[1] Although the majority of cases are non-invasive and can be managed with tumor removal and close surveillance, approximately one in four patients will present with muscle-invasive (T2-T4) bladder cancer (MIBC). Historically, the most common curative-intent treatment for MIBC in the United States has been radical cystectomy with or without neoadjuvant or adjuvant cisplatin-based chemotherapy.[2]

An alternative to cystectomy-based treatment is a bladder-sparing treatment approach involving trimodality therapy (TMT). TMT consists of maximal transurethral resection of the bladder tumor (TURBT) followed by concurrent chemotherapy and bladder-directed radiation.[3] Randomized data comparing cystectomy-based treatment to bladder-sparing TMT are lacking, but long-term outcomes of patients managed with high-quality TMT compares favorably with cystectomy-treated patients.[4, 5]

Several studies have demonstrated that the addition of concurrent chemotherapy to radiation improves disease outcomes in MIBC patients undergoing TMT.[4-7] Cisplatin-based chemotherapy is often favored in this context; however, a significant fraction of MIBC patients are not eligible for cisplatin-based concurrent chemotherapy due to comorbidities such as renal

dysfunction, hearing loss, or peripheral neuropathy. Non-cisplatin based regimens can also be used, but can also be associated with significant toxicity.[8, 9]

A significant percentage of MIBC patients develop recurrent or metastatic disease despite aggressive therapy. Metastatic bladder cancer remains a lethal disease, and little progress has been made in the past several decades in improving outcomes for patients with metastatic bladder cancer. The recent discovery and clinical implementation of immunotherapy has transformed the management of metastatic bladder cancer, and five immune checkpoint inhibitors are now approved for use in the first-line and/or cisplatin-refractory metastatic setting.[10] However, the role of immune checkpoint blockade in the curative management of non-metastatic bladder cancer – alone or in combination with other agents such as chemotherapy and/or radiation – is unknown.

2.2 IND Agent

Avelumab

Avelumab is a fully human IgG1 monoclonal antibody directed against programmed death-ligand 1 (PD-L1), a transmembrane receptor expressed on tumor and immune cells. PD-L1 binds to programmed death 1 (PD-1) on activated T cells and acts as a negative regulator of the host immune response.

Avelumab is FDA-approved for the treatment of metastatic Merkel cell carcinoma (mMCC) and platinum-refractory metastatic urothelial carcinoma.[11] Clinical trials in other disease settings are on-going.[12, 13] The approved dose is 10 mg/kg as an intravenous infusion over 60 minutes every two weeks.[11]

2.3 Other Agent(s)

Radiation

Therapeutic radiation is a mainstay of cancer treatment, and it is estimated that nearly two-thirds of cancer patients will receive radiation at some point during their disease course.[14] Advances in imaging and dosimetry allow for precise delivery of higher radiation doses to the target while minimizing radiation to the surrounding normal tissues.

Radiation is used in both the curative and palliative treatment of bladder cancer.[2] For patients with non-metastatic MIBC, radiation is a critical component of trimodality therapy (TMT), as outlined in Section 2.1.[4, 5] In this setting, radiation is typically delivered to the bladder and adjacent lymph nodes, with the bladder tumor bed receiving a total dose of 55-65 Gray (Gy).

2.4 Rationale

Optimal treatment for MIBC involves either cisplatin-based neoadjuvant chemotherapy followed by cystectomy or bladder-sparing TMT with concurrent cisplatin-based chemoradiotherapy.[3] However, a significant percentage of MIBC patients are ineligible for cisplatin-based

chemotherapy due to poor renal function or other medical comorbidities.

For MIBC patients who are not candidates for cisplatin-based chemotherapy, treatment options include cystectomy followed by investigational non-cisplatin-based chemotherapy or immunotherapy. However, many patients who are not candidates for cisplatin-based chemotherapy are also poor candidates for cystectomy (or refuse cystectomy).

An alternative treatment option for cisplatin-ineligible MIBC patients is bladder-sparing trimodality therapy involving bladder-directed radiation with or without concurrent non-cisplatin-based chemotherapy such as 5-fluorouracil/mitomycin C (5FU/MMC), gemcitabine, or carboplatin/paclitaxel. The addition of 5FU/MMC to bladder-directed radiation has been shown in a randomized setting to improve locoregional disease-free survival, but did not improve overall survival.[7] Non-randomized studies investigating other non-cisplatin regimens such as single-agent gemcitabine or paclitaxel have been reported, and significant chemotherapy-related toxicity can occur.[6, 9]

Avelumab is a PD-L1 inhibitor shown to be effective in advanced solid tumors, including bladder cancer.[11] Although avelumab has been shown to be active in the metastatic setting, the impact of PD-L1 blockade in the treatment of non-metastatic disease is not known. In cisplatin-ineligible MIBC patients, the use of checkpoint inhibitors such as avelumab is of great interest because PD-L1 blockers may be better tolerated than conventional (cytotoxic) chemotherapy.

Combining radiation with PD-L1 blockade in MIBC is an attractive therapeutic strategy because an increasing body of pre-clinical evidence suggests that PD-L1 blockade can synergize with radiation to improve both local (in the radiation field) and distant (outside the radiation field) disease control. Radiation has been shown to have numerous immunostimulatory effects on the tumor and microenvironment, including a dose-dependent upregulation of MHC class I and co-stimulatory molecules such as CD70 and CD86 on dendritic cells. In addition, radiation activates chemokine release, promotes cross-presentation of tumor antigens, and attracts tumor-infiltrating lymphocytes.[15] Numerous cases of systemic disease response following focal radiation (the so-called ‘abscopal effect’) in patients receiving an immune checkpoint inhibitor have been reported.[16] Additionally, PD-L1 inhibitors have an excellent therapeutic index compared to chemotherapy, which is desirable when treating this population with comorbidities and suboptimal performance status.

Importantly, radiation has been shown to increase PD-L1 expression on tumor cells, and this inhibitory effect can be overcome with immune checkpoint blockade.[17, 18] Radiation and immune checkpoint blockade activate the immune system in non-redundant mechanisms[19], suggesting that combining radiation with PD-1/PD-L1 blockade represents a promising therapeutic strategy.

Despite compelling pre-clinical evidence, clinical experience with combining radiation and PD-L1 blockade is limited. The non-cisplatin-eligible MIBC clinical setting is particularly well-suited for investigating the safety and efficacy of combining radiation and PD-L1 blockade. A significant fraction of newly-diagnosed MIBC patients are not eligible for cisplatin-based

therapy, and there is no randomized evidence demonstrating an overall survival advantage with addition of any systemic agent to bladder-directed radiation in this population. Currently, these patients are treated with radiation alone or with radiation and concurrent cytotoxic chemotherapy (which can be associated with significant toxicity). Therefore, combining radiation with PD-L1 blockade may provide this patient population with an alternative treatment option that is safe and effective.

We hypothesize that avelumab in combination with standard radiation for non-metastatic MIBC is both safe and effective. This trial is designed to test this hypothesis, with the primary goal of assessing the rate of complete clinical response at 3 months following completion of radiation.

2.5 Correlative Studies Background

Planned correlative studies are aimed at elucidating the cellular effects of combined immune checkpoint blockade and radiation as well as identifying biomarkers of therapy response and resistance.

Correlative studies performed on tumor tissue (pre-treatment tumor biopsy obtained at the time of diagnosis from all patients as well as biopsy of residual/recurrent muscle-invasive bladder tumor obtained during standard of care follow-up for patients who fail treatment):

1. *Evaluation of PD-L1 expression by immunohistochemistry (IHC).* PD-L1 staining has been associated with response to immune checkpoint blockade in several disease settings.[20]
2. *IHC analysis of immunologic markers for T-cell subsets (CD3, CD4, CD8, PD-1, FoxP3), B cells, myeloid cells, and other targetable checkpoint receptors and ligands including PD-L2, Tim-3, and Lag-3*. The presence of specific T cells including CD4+ and CD8+ cells has been correlated with improved response to immune checkpoint blockade, whereas other receptors such as FoxP3 (a marker of Tregs) are associated with immune suppression.[21]
3. *Sequencing analysis of T cell receptor (TCR) diversity*. TCR clonality has been associated with anti-PD-L1 response.[22]
4. *Whole exome sequencing (WES).*
5. *Immune-related gene expression signatures (RNAseq and/or NanoString)*.

Correlative studies performed on plasma (P) and/or urine (U):

1. Whole exome sequencing of peripheral mononuclear cells for germline analysis (P)
2. Evaluation of circulating immune cells including T-cell subsets, B cells, and myeloid cells by flow cytometry (P)
3. T cell receptor (TCR) diversity (P)
4. Ultra-low pass whole genome sequencing (ULP-WGS) of tumor cell-free DNA (P, U)

The overall principal investigator may allow the specimens collected at DFCI to be sent to other facilities for future analysis. Investigators, including investigators from collaborating institutions, can request this data and samples for new research.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

Subjects must meet all of the following applicable inclusion criteria to participate in the study. Baseline clinical and laboratory evaluations are to be conducted within 28 days prior to registration. If these screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline C1D1 values. Scans must be done within 28 days prior to start of therapy

1. Histologically confirmed transitional cell (urothelial) carcinoma of the bladder that is invasive into the muscularis propria (≥T2 disease) within 6 months of enrollment date. The presence of variant histologies (squamous, adenocarcinoma, micropapillary, etc.) is allowed. Note: A prior diagnosis of non-muscle-invasive bladder cancer (≤T1) managed with transurethral resection with or without intravesicular therapy (now with muscle invasion) is allowed
2. Male or female subjects aged ≥18 years
   Value: _____
3. ECOG performance status ≤2 or Karnofsky score ≥60% (see Appendix A)
   Value: _____
4. Life expectancy of greater than 1 year
5. Demonstrate normal organ and marrow function as defined in the table below.

System	Laboratory Value Requirement	Patient Value
Hematological:		
Hemoglobin	>9 g/dL	
Platelet count	>100,000 per mm3	
Leukocyte count	>3,000 per mm3	
Absolute neutrophil count (ANC)	>1,500 per mm3	
Hepatic:		
Total bilirubin*	<1.5 x ULN	
Aspartate aminotrasferase (AST)	<2.5 x ULN	
Alanine aminotransferase (ALT)	<2.5 x ULN	

*For patients with Gilbert's syndrome, if total bilirubin is >1.5 x ULN, direct bilirubin must be <1.5 x ULN

6. Estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula.
   Value: _____

7. Inability to receive cisplatin-based chemotherapy, as defined by creatinine clearance <60 ml/min, ECOG PS ≤2, grade 2 or higher hearing loss, NYHA class 3 or higher, neuropathy (grade 2 or higher), or patient refusal to receive cisplatin-based chemotherapy.
8. Women of child-bearing age must have a negative serum pregnancy test at screening.
9. Women of child-bearing potential and men must agree to use a highly effective method of contraception (hormonal or barrier method of birth control, or abstinence) beginning prior to study entry, for the duration of study participation, and for at least 30 days after last avelumab treatment administration if the risk of conception exists
10. Ability to start study treatment (first cycle of Avelumab) within 1-8 weeks of the most recent pre-study TURBT.
11. Ability to understand and willingness to sign a written informed consent document

3.2 Exclusion Criteria

Indicate that the subject follows the criteria by checking the boxes below.

12. Prior intravenous therapy for treatment of bladder cancer
13. Prior pelvic radiation
14. Any component of small cell histology in the bladder biopsy
15. Evidence of lymph node involvement or metastatic disease on CT of the chest, abdomen, and pelvis. To be considered positive, a lymph node must measured >15 mm in short axis. Bone scan is recommended in patients with bone pain or elevated alkaline phosphatase. PET/CT can be considered in patients with renal dysfunction who are unable to receive IV contrast
16. Clinically significant (i.e. active) cardiovascular disease: symptomatic congestive heart failure (≥ New York Heart Association Classification Class II), unstable angina pectoris, serious cardiac arrhythmia requiring medication, or CVA/stroke/MI (< 6 months prior to enrollment)
17. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE Grade ≥ 3)
18. Breast feeding women who are unwilling to stop breastfeeding during treatment and for at least one month after the duration of treatment
19. Any concurrent chemotherapy, biologic, or hormonal therapy for cancer treatment
20. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroid, 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) are allowed.
21. Active autoimmune disease requiring systemic immunosuppressive treatment. Patients with controlled autoimmune disease not requiring systemic immunosuppressive treatment including diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid are eligible.
22. History of another malignancy within 5 years prior to randomization except for: non-muscle-invasive bladder cancer (i.e., ≤T1), completed resected basal cell or squamous cell skin cancer, completed resected carcinoma in situ of any site, or localized prostate

cancer managed curatively with a non-radiation based approach
23. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines
24. Major surgery within the last 30 days (with the exception of TURBT).
25. Active and/or uncontrolled infection. The following exceptions apply:
    a. Participants with HIV infection are eligible if they are on effective antiretroviral therapy with undetectable viral load within 6 months, provided there is no expected drug-drug interaction.
    b. Participants with evidence of chronic HBV infection are eligible if the HBV viral load is undetectable on suppressive therapy (if indicated), and if they have ALT, AST, and total bilirubin levels < ULN, and provided there is no expected drug-drug interaction.
    c. Participants with a history of HCV infection are eligible if they have been treated and cured. For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load, and if they have ALT, AST, and total bilirubin levels < ULN."
26. Prior organ transplantation including allogenic stem-cell transplantation
27. Patient is unwilling to stop (or wishes to start) taking herbal and natural remedies that may have immune-modulating effects during the study period
28. Persisting toxicity related to prior therapy (NCI CTCAE Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable
29. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
30. Pregnant women are excluded from this study. Based on its mechanism of action. Avelumab can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to foetal tissue. Human IgG1 immunoglobulins are known to cross the placenta. Therefore, Avelumab has the potential to be transmitted from the mother to the developing foetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. Therefore, potential risks of administering Avelumab during pregnancy include increased rates of abortion or stillbirth. Advise females of reproductive potential to use effective contraception during treatment with Avelumab and for at least one month after the last dose of avelumab.

The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. See section 5.3 for more details.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. Pregnant women are excluded from the trial due to known harms of avelumab to a fetus.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the DF/HCC Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following DF/HCC registration, participants may begin protocol-specific therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy within one month after registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Patients will be enrolled in two stages. In the first stage, 12 patients will be accrued. If there are 5 or fewer responses measured by the 3 month complete clinical response rate in these 12 evaluable patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 24 patients. See Section 13 for more details.

5.1.1 Surgery

All patients should undergo maximal safe transurethral tumor resection of the bladder tumor (TURBT) performed by a urologist. TURBT can be performed before or after trial enrollment. A second TURBT by the same or a different urologist prior to initiation of avelumab is encouraged but not required.

5.1.2 Avelumab

The first cycle of avelumab will begin within 1-8 weeks of the final TURBT.

Avelumab will be administered every 2 weeks, with 14 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Safety will be assessed at each biweekly trial visit and will include assessment of performance status, physical examination, clinical laboratory tests (complete blood count, serum chemistry, hepatic panels, and free T4 and TSH), and documentation of concurrent medications and adverse events. At these visits, labs must be reviewed by study staff prior to treatment to ensure that lab values meet criteria as described below. Other labs (e.g. TSH) which may take longer to obtain results are not required to be reviewed prior to dosing.

The criteria to treat at the beginning of each cycle are:

- Hemoglobin ≥9.0 g/dL (Note: Transfusion to achieve this is allowed)
- Absolute neutrophil count (ANC) 1.5 x 10^9/L (≥ 1500 per mm^3)
- Platelet count ≥100*)* x 10^9/L)
- Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN)
- AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal

If labs were obtained within 72 hours prior to cycles 1-6, they do not need to be repeated on Day 1 of the respective cycle.

Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1.3 Radiation

The radiation planning and treatment process will proceed as follows:

5.1.3.1 Timing:

The radiation mapping CT should take place after the final TURBT has been performed and prior to the first avelumab infusion.

5.1.3.2 Preparation:

Patients should be encouraged to initiate daily Miralax one week prior to the CT and perform a Fleet's enema on the evening before and morning of the CT to facilitate rectal emptying. Patients should drink at least 8 ounces of oral contrast agent one hour prior to the radiation mapping CT. Patients should attempt to empty their bladder immediately prior to the radiation mapping CT.

5.1.3.3 Immobilization:

Patients will be positioned in a stable and comfortable supine position with arms rested on the chest.

5.1.3.4 Radiation CT simulation:

The treatment planning process will include CT based simulation with axial imaging (slice

thickness of 1.25-2.5 mm). The superior border of the CT should be no lower than the L4 vertebral body and the inferior border should be below the ischial tuberosities. Use of intravenous (i.v.) contrast during the CT is optional.

5.1.3.5 Contours:

The GTV (gross tumor volume) includes any remaining gross bladder tumor, the tumor bed (i.e., the portion of the bladder wall initially involved with tumor). Information available from physical examination, cystoscopic bladder mapping, intraoperative reports, and radiographic studies should be used to delineate these structures. Close cooperation with the treating urologist is essential. Cystoscopically placed fiducial markers may be used.

The CTV_tumor includes the GTV plus a 1.0 cm uniform expansion.

The CTV_bladder includes the entire bladder volume (including the bladder wall thickness) plus a 1.0 cm uniform expansion and should be inclusive of the entire CTV tumor.

The CTV_pelvis will include the CTV_bladder, the prostate and prostatic urethra (in men), and the regional lymph nodes. The regional lymph nodes include the perivesciular, internal iliac, external iliac, and obturator lymph nodes from the level of the anterior aspect of the S2-S3 junction superiorly to the lower pole of the obturator foramen inferiorly.

A 5 mm planning tumor volume (PTV) margin will be uniformly added to all CTVs to account for set-up variation.

Conventional or IMRT treatment planning is allowed.

5.1.3.6 Prescription:

Two dose schemes are allowed at the discretion of the treating radiation oncologist:

- Scheme #1 (preferred): 65 Gy in 35 fractions over 7 weeks. PTV_pelvis, PTV_bladder, and PTV_tumor will first receive 45 Gy in 25 fractions. PTV_bladder and PTV tumor will then receive an additional 8 Gy in 4 fractions (for a total PTV_bladder dose of 53 Gy), and then the PTV_tumor will receive an additional 12 Gy in 6 fractions (for a total PTV_tumor dose of 65 Gy).

- Scheme #2 (allowed): 55 Gy in 20 fractions over 4 weeks. PTV_bladder will receive 55 Gy in 20 fractions.

5.1.3.7 Daily Target Localization:

Isocenter or reference point port localization images should be obtained on the treatment unit immediately before each treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices or cone-beam CT equipment.

5.1.3.8 Timing of Radiation Treatment:

Daily radiation treatments will commence within 14 days of C1D1 of avelumab. On the days of

avelumab administration that fall within the 4-7 weeks of daily radiation, participants will receive both radiation treatment and avelumab infusion. Avelumab or radiation may be delivered first, and there is no additional wait time required between administration of avelumab and radiation treatment on those days. Radiation treatments will be delivered daily with the exception of weekends (Saturdays and Sundays) and departmental holidays. Every effort should be made to complete at least four radiation treatments in each seven day consecutive period.

5.1.3.9 Dosimetry:

The minimum dose to each PTV should be no less than 95% of the prescribed PTV dose. At least 99% of each PTV should receive 100% of the prescribed PTV dose. The maximum dose to any PTV should be less than 110% of the prescribed PTV dose.

5.1.3.10 Organs at Risk:

The rectum volume is defined on CT from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. The femoral head volumes include the femurs from their superior extent to the level of the lesser trochanters. The following DVH criteria should be achieved.

Rectum: No more than 50% of the volume above 55 Gy

Femoral heads: No more than 10% of the volume above 50 Gy

5.1.3.11 Planning Priorities:

1. Respect dose limits to organs at risk
2. Achieve PTV coverage

5.1.3.12 Technical Factors:

Conventional linear accelerators or specialized linear accelerators with image guidance (e.g., TrueBeam, Agility, Novalis, Trilogy, Synergy, Artiste) and photon energies of at least 6MV are allowed. These units can be used with 3D-conformal dose delivery or IMRT.

5.2 Agent Administration

5.2.1 Avelumab

Avelumab is administered as a 60 minute (±5 minutes) IV infusion, diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. Administration completion in under 55 minutes is considered a deviation.

Patients will receive 10 mg/kg avelumab via IV infusion every 2 weeks for 6 doses unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

In order to mitigate infusion-related reactions, subjects must be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab.

Premedication should be administered for subsequent avelumab doses if the patient has any Grade 1 or 2 infusion-related reaction as described in Table 2 below or if deemed necessary based upon clinical judgment of the provider.

In the event of infusion-related reactions, treatment should be modified as outlined below:

Table 2. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab 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 closely for 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 avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Patients will be monitored before, during and after the infusion with assessment of vital signs. Patients are monitored (pulse rate, blood pressure) approximately prior to the start of infusion (±5 minutes), 30 minutes from infusion start (±5 minutes), and post infusion completion (±5 minutes) for infusion-related reactions. When infusion rate is slowed or temporarily stopped, or in the event that it is anticipated that administration will take longer than 89 minutes, patients will be monitored at every 30 minute interval (±5 minutes). Following the first avelumab infusion, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions. If no infusion-related reactions are noted in this 30 minute post-infusion period, post-infusion monitoring is not required following subsequent infusions.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

It is important to note for administration that the expiry time of final IP is 24 hours from the time the vials were removed from the refrigerator and allowed to reach room temperature: 24 hours under refrigerated conditions (2-80 °C, 36-46°F) with no more than 8 of those hours at room temperature (15-25°C, 59-77°F), including infusion time.

If either the preparation time or the infusion time exceeds the time limits, a new dose must be prepared from new vials. Avelumab does not contain preservatives, and any unused portion must be discarded.

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, and oxygen should be available for immediate access.

See Section 6.0 for dosing delays/dose modifications.

5.2.2 Radiation

See section 5.1 for radiation planning details. Daily radiation treatments will commence within 14 days of C1D1 of avelumab (i.e., during cycle 1 of avelumab). On days when both an avelumab infusion and radiation are planned (such as C2D1 and C3D1), either avelumab or radiation can be administered first.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of avelumab with other concomitantly administered drugs through the cytochrome P450 system, data capture must include the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Table 1. Permitted concomitant medications

Supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care.	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [excluding palliative radiotherapy])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

Table 2. Excluded concomitant medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly with the study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly with the study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly with the study treatment. (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 at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: - Use of immunosuppressive medications for the management of treatment-related AEs. - Use in patients with contrast allergies. - In addition, use of inhaled, topical and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).
Live attenuated vaccines	Should not be given through 30 days after the last dose of avelumab
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Principal Investigator

5.4 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. In the absence of treatment delays due to adverse event(s), treatment will continue until the prescribed radiation has been delivered and the patient has received 6 cycles of avelumab, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) possibly, probably, or definitely related to the study drug, defined as:

  - Grade ≥3 adverse reaction
  - Persistent Grade ≥ 2 treatment-related adverse reaction that does not recover to Grade 1 or resolve within 30 days after last dose
  - Uveitis grade ≥2
  - For immunologic adverse events that require treatment with corticosteroids: Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 6 weeks
- Participant demonstrates an inability or unwillingness to comply with the treatment regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Avelumab dosing delay of >6 weeks
- Interruption to radiation for any reason that results in ≥5 successive treatments missed

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.5 Duration of Follow Up

Participants will be followed for a minimum of two years after removal from protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Follow-up by telephone is allowed. If patient wishes to transfer care back to local urologist following completion of trial therapy, records will be obtained from the outside urologist if possible.

If a participant is found to have disease progression, the patient will be treated at the discretion of their clinicians and followed via electronic medical record. If protocol assessments are no longer clinically indicated following progression and thus do not occur, they will not result in a deviation or violation.

The following assessments will be performed 10-14 weeks following completion of the radiotherapy: cystoscopy, urine cytology, bladder biopsy of any suspicious areas per standard of care, CT scan (abdominal/pelvic and chest).

Additional follow-up will be performed as per standard of care and should include:

- Post-treatment years 1-2:
  - History/physical every 3 months
  - Laboratory studies (including CBC and CMP) every 3-6 months
  - Cystoscopy and urine cytology every 3 months as clinically indicated

  - CT of abdomen and pelvis (including visualization of the upper tracts) and chest CT (or chest xray) every 3-6 months
  - Adverse event and concomitant medication assessment

- Post-treatment years 3-5:
  - Cystoscopy and urine cytology every 6 months, as clinically indicated
  - CT of abdomen and pelvis (including visualization of the upper tracts) and chest CT (or chest xray) every 12 months, as clinically indicated
  - Laboratory studies as clinically indicated
  - Adverse event and concomitant medication assessment
  - History/Physical exam

- Post-treatment years 6-10:
  - Cystoscopy annually, as clinically indicated
  - Laboratory or imaging studies as clinically indicated
  - Adverse event and concomitant medication assessment
  - History/Physical exam

- Post-treatment years >10:
  - All studies as clinically indicated
  - Adverse event and concomitant medication assessment
  - History/Physical exam

Additional follow-up unique to this study will include:

- Urodynamic evaluation (cystometrogram + uroflow, pressure flow study, or fluorourodynamics study) and AUA symptom score are recommended in the third post-treatment year for patients who still have a native bladder. This will incorporate measures of average and peak urinary flow rate, bladder functional capacity, compliance, and leak pressures (continence).

- The following patient-reported QOL assessments will be administered at enrollment (prior to initiation of avelumab and radiation), near completion of radiation (+/- 7 days of the final radiation treatment), and at each follow-up visit, except the 30 day post treatment follow-up and, 30 day post-treatment safety follow-up after the end of radiation):
  - European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30)[28]
  - FACT-Bladder instruments[29]

5.6 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:
- Lost to follow-up
- Withdrawal of consent for data submission

- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Guidelines for infusion-related reactions are in Section 5.2, Agent Administration.

There are no modifications allowed to the dose of avelumab. However, adjustments to rate of administration are allowed (see Section 5.2).

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Table 3. Management of Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL Colitis: abdominal pain; mucus or blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.

Grade 3 to 4 Diarrhea (Grade 3): Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Diarrhea (Grade 4): Life-threatening consequences; urgent intervention indicated Colitis (Grade 4): Life-threatening consequences; urgent intervention indicated	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1 to 2 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; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1 mg/kg/day methylprednisolone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).

	1 to 2 mg/kg/day methylprednisolone or equivalent Add prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1 to 2 mg/kg/day methylprednisolone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe symptoms; limiting self care ADL; oxygen indicated Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1 to 2 mg/kg/day methylprednisolone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month 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 v5)	**Initial Management**	**Follow-up Management**
Grade 1: AST or ALT > ULN to 3.0 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens:

and/or Total bilirubin > ULN to 1.5 x ULN		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	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3 to 4: AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1 to 2 mg/kg/day methylprednisolone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: 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.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
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 Creatinine increased >1.5 - 3.0 x baseline; >1.5 - 3.0 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 3
Grade 3 Creatinine increased >3.0 x baseline; >3.0 - 6.0 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1 to 2 mg/kg/day methylprednisolone or equivalent.	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.

	Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	Permanently discontinue avelumab therapy upon 3rd Grade 3 event (2nd recurrence).
Grade 4 Creatinine increased > 6.0 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1 to 2 mg/kg/day methylprednisolone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) 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 etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	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 cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1 to 2 mg/kg/day methylprednisolone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: professional.heart.org/en/guidelines-statements		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus) **Hyperthyrodism:** **(Grade 1):** Asymptomatic; clinical or diagnostic observations only; intervention not indicated (Grade 2): Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL **Hypothyroidism:** (Grade 1): Asymptomatic; clinical or diagnostic observations only; intervention not indicated (Grade 2): Symptomatic; thyroid replacement indicated; limiting instrumental ADL **Adrenal insufficiency** (Grade 1): Asymptomatic; clinical or diagnostic observations only; intervention not indicated (Grade 2): Moderate symptoms; medical intervention indicated	Continue avelumab therapy Endocrinology consult 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) **Hyperthyrodism:**	Withhold avelumab therapy Consider hospitalization Endocrinology consult	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression).

(Grade 3): Severe symptoms; limiting self care ADL; hospitalization indicated (Grade 4): Life-threatening consequences; urgent intervention indicated **Hypothyroidism:** (Grade 3): Severe symptoms; limiting self care ADL; hospitalization indicated (Grade 4): Life-threatening consequences; urgent intervention indicated **Adrenal insufficiency:** (Grade 3): Severe symptoms; hospitalization indicated (Grade 4): Life-threatening consequences; urgent intervention indicated	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.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low 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/suppressive 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 methylprednisolone or equivalent) followed by corticosteroids taper during at least 1 month.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate. Permanently discontinue avelumab therapy for recurrent ≥ Grade 3 hypophysitis.

	• Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
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 to 2 mg/kg/day methylprednisolone 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	Permanently discontinue avelumab therapy 1 to 2 mg/kg/day methylprednisolone 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	Permanently discontinue avelumab therapy 1 to 2 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 methylprednisolone 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**	Permanently discontinue 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 Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List for Radiation

Immediate Reactions	**Long-Term Reactions**
Common:	**Common:**
• Tiredness • Bladder spasms (mild to moderate) • Burning on urination (mild to moderate) • More frequent bowel movements • Decreased blood count	• Chronic mildly increased need to empty bladder more often that prior to radiotherapy • Occasional bladder spasm • Males: Sterility • Females: Sterility • Menopause, if premenopausal, decreased vaginal secretions
Uncommon:	**Uncommon:**
• Bowel cramping • Diarrhea • Feel the need to empty bowels with nothing to pass • Dehydration requiring I.V. fluids • Incontinence due to urgency • Need for a bladder catheter • Significant bladder spasm • Significant burning on urination • Hospitalization to control symptoms	• Occasional blood in urine
Rare:	**Rare:**
• Skin reddening and irritation	• Chronic blood in urine requiring treatment • Bothersome need to empty bladder often • Incontinence (usually in patients with prior history of TURBT's) • Rectal or urinary bleeding requiring transfusion
Extremely Rare:	**Extremely Rare:**
• Bladder problems requiring surgery • Bowel problems requiring surgery • Cancers caused by radiation	

7.1.2 Adverse Event List for Avelumab

Refer to the current version of the Investigator's Brochure for detailed avelumab safety and toxicity information.

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy.

Important identified risks for avelumab are immune-mediated adverse reactions and infusion related reactions.

Immune-mediated adverse reactions:

immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies [thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus], nephritis and renal dysfunction, and other immune-mediated adverse reactions [myocarditis, pancreatitis, myositis, hypopituitarism, uveitis, myasthenia gravis/myasthenic syndrome, Guillain-Barré syndrome, sclerosing cholangitis, arthritis, polymyalgia rheumatica and Sjogren's syndrome].

Patients with pre-existing autoimmune disease (AID)

In patients with pre-existing AID, data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased compared to the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Infusion-related Reactions

Possible IRRs are defined based on the following Preferred Terms (PTs) and temporal relationship criteria. Events are divided into reactions versus signs and symptoms:

- Reactions include the PTs infusion-related reaction, drug-hypersensitivity, hypersensitivity, type-1-hypersensitivity and anaphylactic reaction. These PTs should be considered when the onset is on the day of study drug infusion (during or after the infusion) or within 1 day thereafter.

- Signs and symptoms of IRRs include the PTs pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain and urticaria. These PTs should be considered, if the onset occurs on the day of study drug infusion (during or after the infusion) and resolves within 2 days after onset.

7.2 Adverse Event Characteristics

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (definition per International Conference on Harmonisation (ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition or abnormal results of diagnostic procedures, including laboratory test abnormalities.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AE's will be categorized according to the likelihood that they are related to the study drug (s). Specifically, they will be categorized using the following terms:

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

AEs and SAEs will be recorded from the date of randomization until 90 days after the last dose of study treatment due to the potential risk for delayed immune-related toxicities with avelumab. The extended safety follow-up beyond 30 days after last avelumab 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. Reporting of Serious Adverse events will be per DFCI Reporting Policy.

Special Considerations:

- Use of a medicinal product during pregnancy or breastfeeding: reports where embryo, fetus or child may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure),
- Reports of medication errors, uses outside what is foreseen in the protocol, including misuse and abuse of the product,
- Occupational exposure (even if not associated with an adverse event)
- Overdose
- Potential drug induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Serious Adverse Event ("SAE" or "SAEs"):

A SAE is any AE as defined above, which also fulfills at least one of the seriousness criteria below:

- results in death,
- is life-threatening[1)],
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/ incapacity,
- is a congenital anomaly/ birth defect, or
- is otherwise considered as medically important[2)].

[1)] Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.
[2)] Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Adverse Events of Special Interest ("AESI"):

An AESI is an AE of scientific and medical concern specific to EMD Serono's Investigational Product or program, for which ongoing monitoring and rapid communication by Principal Investigator to EMD Serono can be appropriate.

Safety Issues/Concerns:

A safety issue/concern is defined as an important identified risk, important potential risk or important missing information. Safety issues/concerns are events which may occur during the Study, not falling under the definition of SUSARs and consequently not being subject of the reporting requirements for SUSARs. Examples are events related to the conduct of the Study or the development of an investigational medicinal product likely to affect the safety of subjects, such as (but not limited to):

- a major safety finding from a newly completed animal study (such as carcinogenicity),
- recommendations of the Safety Data Monitoring Committee (SMC/DMC), if any, where relevant for the safety of subjects,
- in the case of advanced therapy investigational medicinal products, relevant safety information regarding the procurement or the donor.

Events Not to be considered AEs:

Medical conditions present in a patient and documented at the time of Study enrollment, and that

do not worsen in severity or frequency during the Study, are defined as baseline medical conditions, and are NOT to be considered AE.

7.3 Expedited Adverse Event Reporting

Investigators must report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of treatment on the local institutional SAE Form.

It is the responsibility of each participating investigator to report serious adverse events within 24 hours of knowledge to the Overall PI, Dr. Kent Mouw (at the contact given below), or representative personnel; and submit to DFCI IRB within 10 working days.

Kent Mouw, MD, PhD
617-732-7948
kent_mouw@dfci.harvard.edu
Recording and Transmission of Safety Events:

SAEs (related and non-related), AESIs (if there are any for EMD Serono's Product), Special Considerations and Safety Issues/Concerns shall be sent to EMD Serono in English language for recording in EMD Serono's safety database.

In addition to the participating site submitting the SAE to the Overall PI and local institution via the local institutional SAE form, the information shall be sent to EMD Serono by the DFCI study team via email or facsimile listed below within one (1) business day or three (3) calendar days, whatever comes first, after becoming aware of the event. SAE reporting to EMD Serono should be via the applicable EMD Serono report form for clinical studies (either the serious adverse event and overdose report form, parent-child/fetus adverse event report form, or pregnancy report form depending on the nature of the adverse event). Only the DFCI study team will submit SAE reports directly to EMD Serono.

Fax No.: 781-681-2961
Email address: usdrugsafety@emdserono.com

Please specify in the cover letter:

- Protocol Number and/or Title
- Study Identifier
- Subject Number
- Principal Investigator Name
- Sponsor Name
- (S)AE/Onset Date

7.3.1 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human

Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.** In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Avelumab (MSB0010718C)

8.1.1 Description

Avelumab (MSB0010718C) (Bavencio®) is a fully human monoclonal antibody directed against PD-L1 and has been approved for treatment of metastatic urothelial cancer.

8.1.2 Form

Avelumab (MSB0010718C) drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (IV) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of avelumab (MSB0010718C).

8.1.3 Storage and Stability

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Avelumab (MSB0010718C) must be used within the individually assigned expiry date on the label.

8.1.4 Compatibility

The solution supplied will be diluted with 0.9% (w/v) saline or 5% (w/v) dextrose for intravenous (IV) administration.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the immunotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

EMD Serono will supply avelumab (MSB0010718C) to the investigator as a 20 mg/ml solution for infusion after dilution.

8.1.7 Preparation

The dose of avelumab (MSB0010718C) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique.

Prior to the preparation of the dilution for infusion of avelumab (MSB0010718C), allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

The expiry time of final IP is 24 hours from the time the vials were removed from the refrigerator and allowed to reach room temperature: 24 hours under refrigerated conditions (2-80 °C, 36-46°F) with no more than 8 of those hours at room temperature (15-25°C, 59-77°F), **including infusion time**.

Weight-based dosing (10 mg/kg) will be administered using an IV bag containing commercially available 0.9% (w/v) saline or 5% (w/v) dextrose, with a final avelumab (MSB0010718C) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. DFCI standard of practice for weight based dosing and BSA calculation may be used.

Calculate the dose volume of avelumab (MSB0010718C) needed for the patient to achieve the accurate weight-based dose. To prepare the IV bag remove a volume of diluent equal to the calculated volume of avelumab (MSB0010718C) to be added to the IV bag. The calculated volume of avelumab (MSB0010718C) is then added to an appropriately-sized IV bag such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

8.1.8 Ordering

The study site will order the avelumab (MSB0010718C) from EMD Serono. EMD Serono's internal identifier for this research study is MS100070_0217.

8.1.9 Accountability

The Principal Investigator, or a responsible party designated by the Principal Investigator, should maintain a careful record of the inventory and disposition of avelumab (MSB0010718C) using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. Certificates of delivery must be signed. The date, quantity and batch or code number of avelumab (MSB0010718C), and the identification of patients to whom study drug has been dispensed by patient number and initials will be included.

8.1.10 Destruction and Return

The Principal Investigator shall not make avelumab (MSB0010718C) available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow avelumab (MSB0010718C) to be used in any manner other than that specified in this protocol. Any unused portion of avelumab (MSB0010718C) left in a vial may be destroyed as per institutional standard of practice (SOP).

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Rationale
Because determinants of response to immune checkpoint blockade and radiation are poorly understood, we plan to perform comprehensive immunogenomic analyses of patient blood, tumor, and urine samples in an effort to identify predictive biomarkers. All planned biomarker and laboratory-based correlative studies are ancillary/exploratory.

Correlative studies are planned for the following specimens:

- pre-treatment muscle-invasive tumor biopsy
- post-treatment residual or recurrent muscle-invasive tumor (when available)
- blood (including peripheral blood mononuclear cells and plasma)
- urine

All specimens for biomarker and correlative studies will be stored in the Gelb Center at DFCI. Specimens collected at Beth Israel Deaconess Medical Center will be transferred, processed by

and stored in the Gelb Center at DFCI. Documentation of specimen transfer will be recorded for each sample on an IRB-approved transfer log.

Pre-treatment/post-treatment tumor

All analyses will be performed on biopsy specimens that are collected during routine clinical care. No additional biopsy procedures will be performed for the planned translational biomarker studies, and no additional tissue will be harvested beyond what is collected as part of routine clinical care. The timing of the collection and use of biopsy specimens will be at the discretion of the overall PI.

Formalin-fixed paraffin-embedded (FFPE) tissue from the pre-treatment muscle-invasive tumor biopsy will be collected for all patients. For patients who have an incomplete response to avelumab plus radiation or who experience a tumor recurrence at any time following treatment, FFPE tumor and normal tissue from the residual/recurrent muscle-invasive tumor biopsy (and/or cystectomy specimen) will also be collected for analysis.

We will use immunohistochemistry to analyze PD-L1 expression as well as immune cell subsets including CD3+, CD4+, CD8+ T-cells. PD-L1 expression and immune cell infiltration have been identified as potential predictors of response to immune checkpoint blockade in other clinical contexts[23]; however, these associations have not been characterized in the context of combined immune checkpoint blockade and radiation for muscle-invasive bladder cancer.

Whole exome sequencing (WES) will be performed on all available tumor specimens to determine mutational burden, neoantigen profile, and mutational status of known bladder cancer genes.[24] For each FFPE tumor sample, genomic DNA will isolated in the Mouw laboratory using a commercially available kit. WES will be performed at the Broad Institute.

Whole transcriptome RNA sequencing (RNAseq) will be performed to evaluate transcriptional profiles of tumor and infiltrating immune cells. RNA will be isolated using a commercially available kit. RNA sequencing will be performed at the Broad Institute. For cases in which RNAseq is not feasible, Nanostring cancer and immune gene expression analysis will be performed at DFCI or BWH.

Other tumor immunogenomic studies as deemed feasible and informative by the principal investigators may also be performed.

Peripheral blood

Pre-treatment peripheral blood samples will be collected for all patients. In addition, a blood sample will be collected near the end of radiation (+/-5 days from the date of last radiation treatment), and at the End of radiation follow-up visit follow-up visit.

At each blood collection time point 2 purple tops, 2 red tops, and 1 PBMC tube will be collected. All samples will be de-identified and labeled with the participant's initials, participant's study ID

number, date of collection, and time point ("pre-treatment", "on-treatment", "3 mo post-treatment"). Unless otherwise specified, samples will be processed and stored in the Gelb Center at DFCI.

From the pre-treatment blood sample, genomic DNA for WES will be isolated from peripheral mononuclear cells using a commercially available kit.

Ultra-low pass whole genome sequencing (ULP-WGS) and/or deep targeted sequencing of cell-free DNA (cfDNA) will be performed on pre-treatment, end-of-treatment, and 3 month post-treatment blood specimens. If tumor cfDNA is detectable at sufficient levels, WES of cfDNA will be performed.

Cytokine profiling using Luminex technology will be performed using plasma samples from pre-treatment, end-of-treatment, and 3 month post-treatment blood specimens.

T cell receptor (TCR) sequencing will be performed on pre-treatment, end-of-treatment, and 3 month post-treatment blood specimens.

Other blood-based studies as deemed feasible and informative by the principal investigator may also be performed.

Urine

A pre-treatment urine sample will be collected for all patients. In addition, a urine sample will be collected near the end of radiation (+/-5 days from the date of last radiation treatment), and at the end of radiation follow-up visit.

Urine samples will be processed as follows:

1. Collect >50 ml urine sample in 100 ml container
2. Divide half of sample into 4-8 ml aliquots
3. Transfer other half into a 50 ml tube and spin the tube at 2500 rpm for 10 min then aliquot supernatant as above
4. Re-suspend the pellet in 2 ml 1xPBS, split into two 1.5 ml Eppendorf tubes, and centrifuge at >10,000g for 5 minutes, then remove the supernatant.
5. All urine specimens will be stored in a -80°C freezer in the Gelb Center at DFCI.

Ultra-low pass whole genome sequencing and/or deep targeted sequencing of cell-free DNA (cfDNA) will be performed at Fox Chase Cancer Center for all pre-treatment, on-treatment, and 3 month post-treatment urine samples. If tumor cfDNA is detectable at sufficient levels, whole exome sequencing from cfDNA will be performed.
Other urine-based studies as deemed feasible and informative by the principal investigators may also be performed.

9.1 Biomarker Studies

Immunohistochemistry/Immunofluorescence

Immunohistochemical (IHC) analysis will be performed on unstained FFPE slides from all available primary and residual/recurrent tumor specimens to determine intratumoral and stromal PD-L1 (CD274), expression and infiltration of CD3+/CD8+ and CD3+/CD4+ T-cells. In addition, multiplex immunofluorescence (IF) will be used to score the tumor microenvironment for integrated expression of PD-1, PDL1, PD-L2, CD3, CD4, and CD8. For these IHC and IF studies, up to 10 unstained FFPE slides may be requested.

These planned IHC and IF studies are designed to evaluate the immunomodulatory effects of radiotherapy in combination with anti-PD-L1 therapy. Tumor PD-L1 expression has been linked to response rates of PD-1 checkpoint blockade.[25] Pre-clinical data suggests that radiotherapy may upregulate intratumoral PD-L1 expression, and that this upregulation can be overcome with anti-PD-L1 therapy.[18] However, little is known about how the pattern of expression (i.e. tumor cells vs. infiltrating immune cells) impacts response, particularly in bladder cancer.

The purpose of these studies is to investigate if PD-L1 expression as a biomarker of response in patients treated with radiotherapy plus avelumab and to evaluate the effects of radiotherapy plus avelumab on PD-L1 expression. We hypothesize that patients with detectable PD-L1 expression will be more likely to respond to therapy. We further hypothesize that PD-L1 expression will increase in patients who fail to have a complete clinical response to radiation plus avelumab at 3 months following completion of radiotherapy. Exclusion of T-cells in the tumor microenvironment has also been linked with lack of response to checkpoint inhibition the planned studies will examine the density and subtype of tumor-infiltrating lymphocytes using markers such as CD3, CD4, and CD8.

As described above, based on prior preliminary studies conducted in patients across several disease types, PD-L1 expression and greater numbers of infiltrating lymphocytes may predict response to PD-1 / PD-L1 inhibitors in certain settings.[22] However, the biologic activity of PD-1 / PD-L1 inhibitors suggest that expression of PD-1 on tumor-infiltrating lymphocytes and PD-L2 on tumor-infiltrating lymphocytes and tumor immune cells could also be valuable predictive biomarkers.[25] Additionally, spatial resolution may be of importance; co-localization of multiple protein biomarkers on the surface of tumor cells or tumor-infiltrating lymphocytes could add extra diagnostic and predictive value, especially when the amount of tissue available for analysis is limited.

9.1 Laboratory Correlative Studies

Consented subjects processing and collection of tissue will be collected under the GELB protocol (DFCI Protocol #15-349). Urine and blood will be collected under either the GELB protocol OR this research protocol.

DNA sequencing
Whole exome sequencing (WES) will be performed for all available primary and residual/recurrent tumor samples. WES of germline DNA will also be performed from

peripheral blood mononuclear cells (PBMCs). For urine and plasma samples with detectable cfDNA, WES will be performed.

In addition to determining the mutational status of known bladder cancer genes, WES will also allow us to calculate tumor mutational burden and neoantigen load, which have been associated with response to checkpoint blockade.[26]

T cell receptor (TCR) sequencing will be performed from each pre-treatment tumor, from residual tumor and adjacent lymph nodes (when available from patients with residual/recurrent disease following protocol therapy), and pre-treatment, on-treatment, and post-treatment blood samples.

RNA sequencing

Whole transcriptome RNA sequencing (RNAseq) will be performed from available tumor samples to determine the transcriptional features of the tumor as well as peri-tumoral immune cells. Genes examined will include known bladder cancer drive genes as well as cytokines, chemokines, markers of T-cell exhaustion, and canonical pathways of immune activation or suppression.[27] RNAseq will be used to identify infiltrating immune cell populations using deconvolution techniques and also confirm expression of predicted neoantigens.

Flow cytometry

Flow cytometry will be performed from available PBMCs to provide a detailed examination of immune cell subsets and functionality.

10. STUDY CALENDAR

	Screening (28 day period prior to Registration)	Cycle 1 Day 1[2,**]	Cycle 2 Day 1 (± 2 days)	Cycle 3 Day 1 (± 2 days)	Cycle 4 Day 1 (± 2 days)	End of Radiation (± 7 days)	Cycle 5 Day 1 (± 2 days)	Cycle 6 (± 2 days)	30 day post-treatment safety follow-up (+/- 7 days)	End of radiation follow up (70-96 days post RT))[7]	Follow up[14 7]	Follow up[15]	Follow up[16] =	Post-treatment years >10[6]
Sign Informed Consent	X													
History/Physical Exam	X	X	X	X	X		X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X		X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X		X	X	X	X	X	X	X	X
Adverse event reporting		X	X	X	X		X	X	X	X	X	X	X	X
Avelumab		X	X	X	X		X	X						
Serum pregnancy test	X	X		X			X							
Radiation[1]		X	X	X	X									
CBC w/ diff	X	X	X	X	X		X	X	X	X	X[4]	X[6]	X[6]	X
Complete Metabolic Panel	X	X	X	X	X		X	X	X	X	X[4]	X[6]	X[6]	X
HBV, HCV	X													
Creatinine clearance	X													
Free T4 and TSH	X				X			X	X	X				
Research Blood Collection		X[12]				X[3]				X[13]				
Urine Sample		X[12]				X[3]				X[13]				
QLQ-C30		X[12]				X					X	X	X	X
FACT-Bladder		X[12]				X					X	X	X	X
AUA Symptom Score		X[12]										X[8]		

Urodynamic Evaluation												x[8]		
Cystoscopy and Urine Cytology										x	x[6]	x[6]	x[6]	x[6]
CT of the Abdomen /Chest/Pelvis[9]	x									x	x[4]	x[5]	x[6]	x[6]
Chest X-Ray											x[10]	x[10]	x[6 10]	x[6 10]
TURBT	x[11]									x[6]	x[6]	x[6]	x[6]	x[6]
Biopsy										x[6]	x[6]	x[6]	x[6]	x[6]

[1] Radiation to commence within 14 days of C1D1. On days when both an avelumab infusion and radiation are planned (such as C2D1 and C3D1), either avelumab or radiation can be administered first

[2] The first cycle of avelumab will begin within 1-8 weeks of the final TURBT

[3] Collected +/- 5 days from the last day of radiation for correlative studies. See section 9.

[4] Every 3-6 months

[5] Every 12 months

[6] Assessments only done as clinically indicated

[7] If the appointment windows for End of Radiation follow up and the 1st post treatment follow up align, appointments can be combined as one.

[8] Urodynamic evaluation (cystometrogram + uroflow, pressure flow study, or fluorourodynamics study) and AUA symptom score are recommended in the third post-treatment year for patients who still have a native bladder

[9] A PET/CT that includes the chest, abdomen, and pelvis can also be used, a urogram/chest CT should be performed if feasible, but is not required.

[10] Can be used in place of Chest CT, otherwise not required

[11] Can be performed before or after trial enrollment

[12] Must be obtained prior to infusion, can happen any time between consent and first infusion.

[13] Blood and urine research specimens collected at the End of Radiation Follow Up

[14] Years 1-2 (Every 3 Months (± 14 days)

[15] Years 3-5 (Every 6 Months (± 28 days)

[16] Years 6-10 (Every Year (± 28 days)

** Labs 3 days before start of treatment do not need to be repeated.

11. MEASUREMENT OF EFFECT

11.1.1 Definitions

Complete Response (CR): Patients will be considered as having a clinical complete response when all biopsies are negative for tumor. A urine cytology specimen that is not positive for malignant cells is also required. Patients with borderline enlarged pelvic lymph nodes that do not meet RECIST criteria (i.e., >1 cm in short axis but <1.5 cm in short axis) must have shrinkage of the node to <1 cm in short axis). In this trial, pelvic lymph nodes are defined as those included in the radiation treatment field (see Section 5.1.3.5).

Partial Response (PR): A PR requires all response criteria for a CR with the exception of either a urine cytology that is positive for malignant cells or Ta/Tis tumor present in a bladder biopsy specimen.

No Response (NR): NR is defined as the presence of the tumor (≥T1) in the tumor-site biopsy specimen.

Progressive Disease (PD): PD is defined as an increase of 50% or more in the largest diameter of the endoscopically appreciable tumor in the tumor-site biopsy specimen, the development of new bladder tumors (≥T1), or the development of metastatic disease.

Distant metastasis (DM): The first appearance of disease in a lymph node, solid organ, or bone. This may be identified on routine follow-up imaging or on a study performed to evaluate a specific patient complaint. Additional radiographic studies or biopsies may be performed at the discretion of the treating physician in equivocal cases but are not required. Radiographic evidence of metastasis is sufficient for evaluation of this endpoint. Time to development of distant metastasis will be defined as the time from the start of protocol therapy to the first appearance of distant metastasis.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions in the bladder are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) by a urologist. Measurable non-bladder lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) and are ≥20 mm by chest x-ray or ≥10 mm on CT scan, MRI, or with calipers on clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest

diameter <10 mm or lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease.

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold

scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if it can be documented that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response

when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Bladder Tumor and Pelvic Lymph Nodes

Complete Response (CR): Patients will be considered as having a clinical complete response when all biopsies are negative for tumor. A urine cytology specimen that is not positive for malignant cells is also required. Patients with borderline enlarged pelvic lymph nodes that do not meet RECIST criteria (i.e., >1 cm in short axis but <1.5 cm in short axis) must have shrinkage of the node to <1 cm in short axis). In this trial, pelvic lymph nodes are defined as those included in the radiation treatment field (see Section 5.1.3.5).

Incomplete response: Any response other than a CR. See sections 11.1.1 and 11.1.2 for additional definitions.

11.1.4.2 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e., not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor; for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and, if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.5 Duration of Response

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without progressive disease or death are censored at the last disease evaluation.

11.1.6 Local Control

Local control is defined as lack of biopsy-proven invasive (≥T1) recurrence in the bladder. Non-invasive bladder recurrences (Ta/Tis) are not considered local failure and can be managed conservatively with transurethral resection with or without intravesicular therapy.

11.1.7 Locoregional Control

Locoregional control is defined as lack of biopsy-proven invasive (≥T1) recurrence in the bladder and lack of imaging evidence of a pathologically enlarged lymph node within the radiation field (see Section 5.1.3.5 for anatomic boundaries of pelvic radiation field).

11.1.8 Metastasis-free survival

Metastasis-free survival is defined as the time from start of protocol therapy to the date of development of disease outside of radiation field (bladder or radiated portion of the pelvis; see Section 5.1.3.5 for anatomic boundaries of pelvic radiation field), such as disease in a non-radiated lymph node, a solid organ, or bone. This may be identified on routine follow-up imaging or on a study performed to work-up a specific patient complaint. Additional radiographic studies or biopsies may be performed but are not required. Radiographic evidence of metastasis is sufficient for evaluation of this endpoint. Participants without events reported are censored at the last disease evaluation.

11.1.9 Cystectomy-free Survival

Cystectomy-free survival is defined as the time from start of protocol therapy to the date of cystectomy for any reason (progressive disease, toxicity, etc). Participants without events reported are censored at the last disease evaluation.

11.1.10 Progression-Free Survival

Progression-free survival is defined as the time from start of protocol therapy to the date of disease recurrence, defined as biopsy-confirmed invasive (≥T1) disease in the bladder, or radiographic and/or pathologic evidence of disease in a lymph node or a metastatic site, or death, whichever comes first. Participants without events reported are censored at the last disease evaluation.

11.1.11 Overall Survival

Overall survival is defined as the time from start of protocol therapy to the time of death from any cause. Participants without events reported are censored at the date last known to be alive.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

Bladder-preserving trimodality therapy (TMT) consisting of maximal transurethral resection of the bladder tumor (TURBT) followed by concurrent chemoradiotherapy is an acceptable alternative to radical cystectomy-based therapy for muscle-invasive bladder cancer (MIBC).[2] The addition of cisplatin-based chemotherapy to radiation improves disease outcomes compared to radiation alone; however, a subset of MIBC patients are not eligible for cisplatin-based chemotherapy.[4] Non-cisplatin based concurrent chemotherapy regimens are also available, but these regimens can be associated with significant toxicity and none have been shown to improve overall survival compared to radiation alone.[8, 9]

In RTOG 0524, a recently published multi-institutional study of non-cisplatin based TMT for cystectomy-ineligible MIBC patients, 70% of patients completed the planned course of

chemoradiotherapy.[9] Among the patients who completed chemoradiotherapy, the 3 month complete clinical response rate was 60%.

Immune checkpoint inhibitors (anti-PD1 and anti-PD-L1 agents) are active in cisplatin-ineligible patients with metastatic bladder cancer[30]; however, the role of immune checkpoint inhibitors in non-metastatic bladder cancer is unknown.

13.1 Study Design/Endpoints

13.1.1 Primary Endpoint

The primary endpoint in this study is the 3-month complete clinical response rate. This evaluation is performed at 3 months (10-14 weeks) from the date of the last radiation treatment. A complete response requires that all biopsies are negative for tumor and that a urine cytology specimen is not positive for malignant cells. See Section 11.1.1 for definition.
.
The historical 3-month complete response rate is based on published data from RTOG 0524, a recently reported multi-institutional study of TMT for cystectomy-ineligible MIBC patients. Although cystectomy-ineligibility is not required for this current trial, the characteristics of patients who are cystectomy-ineligible and those who are cisplatin-ineligible are often closely correlated (i.e., many cisplatin-ineligible patients are often also poor cystectomy candidates). In contrast, many TMT trials that use concurrent cisplatin-based chemotherapy enroll patients who are likely to be significantly healthier than the patients who are likely to enroll on this trial.

Across the two arms of RTOG 0524 (paclitaxel plus radiation or paclitaxel/traztuzumab plus radiation), 70% of patients completed the planned radiation course. Of these patients, 62% had a complete response at 3 months. Therefore, the complete response rate among all enrolled patients was 0.7 x 0.62 = 0.43, or 43%.

We hypothesize that the combination of avelumab and radiation will result in an improvement in the 3-month complete response rate following completion of radiotherapy.

13.1.2 Secondary endpoints

13.1.2.1 Overall survival: Overall survival is defined as the time from start of protocol therapy to the time of death from any cause. Participants without a death event reported are censored at the date last known to be alive. Participants without a death event or who are lost to follow up will be censored at the last date of known follow-up.

13.1.2.2 Progression-free survival: Progression-free survival is defined as the time from start of protocol therapy to the date of disease recurrence, defined as biopsy-confirmed invasive (≥T1) disease in the bladder, or radiographic and/or pathologic evidence of disease in a lymph node or a metastatic site, or death, whichever comes first. Participants without PFS events reported are censored at

the last disease evaluation.

13.1.2.3 Metastases-free survival: Metastasis-free survival is defined as the time from start of protocol therapy to the date of development of radiographic and/or pathologic evidence of disease outside the radiation field, or death, whichever comes first. Participants with MFS events reported are censored at the last disease evaluation.

13.1.2.4 Locoregional control: Locoregional control is defined as lack of biopsy proven invasive (≥T1) recurrence in the bladder and lack of imaging evidence of a pathologically enlarged lymph node within the radiation field.

13.1.2.5 Quality-of-life (QOL): Patient-reported quality of life (QOL) data will be collected longitudinally using two validated QOL instruments (QLQ-C30 and FACT-Bladder questionnaires).

13.1.3 Exploratory Endpoints

13.1.3.1 Genomic alterations: Whole exome sequencing of tumor and matched germline DNA will be performed. Copy number and mutational events will be identified and genomic features will be correlated with clinical data.

13.1.3.2 Gene expression: Whole transcriptome RNAseq will be performed and gene expression-based subtying and gene set enrichment analysis will be performed.

13.1.3.3 Immune features: Tumor immune features will be characterized by immune-based IHC and TCR sequencing, and results will be correlated with clinical data.

13.1.3.4 Urine-based biomarkers: Pre-treatment and post-treatment urine samplese will be collected and urine cell-free DNA analysis will be performed. Results will be correlated with clinical data.

13.1.4 Study Design

Simon's two-stage minimax design will be applied.[31] The null hypothesis that the true response rate is 0.43 will be tested against a one-sided alternative. In the first stage, 12 patients will be accrued. If there are 5 or fewer responses measured by the 3 month complete clinical response rate following completion of radiotherapy in these 12 evaluable patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 24. The null hypothesis will be rejected if 15 or more responses are observed in 24 patients. This design assumes a type I error rate of 0.05 and power of 80% when the true response rate is 0.68. The probability of early stopping is 0.56. All patients with intent-to-treat are evaluable patients.

Accrual pause period: As the complete clinical response rate is evaluated at 3 months from the date of last radiation treatment, there will be a "accrual pause period" of maximum 4 months (3 month for the maturity of the last patient enrolled in first stage plus maximum of 1 month for data evaluation period) after the 12th patient (the last patient) in the first stage completes radiation, and a decision will be made whether accrual will be continued to second stage or not based on the decision rule described above.

13.2 Sample Size, Accrual Rate and Study Duration

The total sample size will be 24 (12 patients in the first stage and 12 patients in the second stage if continued) as described above. The expected accrual rate is one patient per month. The trial will be conducted over 32 months.

Accrual Targets						
Ethnic Category	**Sex/Gender**					
	Females		**Males**		**Total**	
Hispanic or Latino	2	+	4	=	6	
Not Hispanic or Latino	5	+	13	=	18	
Ethnic Category: Total of all subjects	7 (A1)	+	17 (B1)	=	24	(C1)
Racial Category						
American Indian or Alaskan Native	0	+	0	=	0	
Asian	0	+	1	=	1	
Black or African American	1	+	2	=	3	
Native Hawaiian or other Pacific Islander	0	+	1	=	1	
White	6	+	13	=	19	
Racial Category: Total of all subjects	7 (A2)	+	17(B2)	=	24	(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

We target the accrual of the trial to match the ethnic breakdown of the state of Massachusetts, which was estimated by the US Census Bureau in 2013 to be 75.1% non-Hispanic White, 10.5% Hispanic, 8.1% Black, 6.0% Asian, 0.5% Native American, 2.1% with two or more races, and 0.1% other.

13.3 Stratification Factors

Patients will not be stratified.

13.4 Interim Monitoring Plan

No interim monitoring will be performed.

13.5 Analysis of Primary Endpoints

The primary analysis will be an evaluation of 3-month complete clinical response rate for all patients (intent-to-treat population) that started treatment. No replacement will be performed for any patients who were removed from the trial after initiating treatment. Exact proportions and 95% confidence intervals for 3-month complete clinical response rate will be provided.

13.6 Analysis of Secondary Endpoints

13.6.1 Overall survival

Overall survival is defined as the time from start of protocol therapy to the time of death from any cause. Overall survival (OS) will be evaluated with Kaplan-Meier curves methods and Cox regression Patients without a death event will be censored at the date last known to be alive. See section 11.1.11 for definition.

13.6.2 Progression-free survival

Progression-free survival (PFS) will be evaluated with Kaplan-Meier curve methods and Cox regression. PFS is defined as the time from the start of protocol treatment to progression or death due to any cause. Patients without a PFS event will be censored at the date of last disease evaluation for progression.

13.6.3 Locoregional control

Locoregional control will be calculated as the percentage of evaluable patients with lack of biopsy-proven invasive (≥T1) recurrence in the bladder and lack of imaging evidence of pathologically enlarged lymph node within the radiation field at the time of the first post-treatment assessment (10-14 weeks following completing of radiation).

13.6.4 Quality-of-life

Patient-reported quality of life (QOL) data will be collected longitudinally using two validated QOL instruments (QLQ-C30 and FACT-Bladder questionnaires). QOL data will be analyzed using linear models for repeated measures data.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.7.2 Evaluation of the Primary Efficacy Endpoint

The primary endpoint will be analyzed on an intent-to-treat basis.

14. PUBLICATION PLAN

The results will be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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