CLINICAL STUDY PROTOCOL

Phase Ib Study of Avelumab Plus Bacille Calmette-Guerin (BCG) in Patients with Non-muscle Invasive Bladder Cancer (ABC Trial)

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Test Products:	Avelumab; Intravesical BCG
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1 BACKGROUND INFORMATION AND STUDY RATIONALE

1.1 Disease Background

Bladder cancer is the one of the most common urologic cancers with an estimated 79,030 new cases and 16,870 death in the United States in 2017 [1]. Of all newly diagnosed cases of bladder cancer, about 70% present as non-muscle invasive bladder cancer (NMIBC), including tumors with stage Ta, T1 and carcinoma in situ (CIS) [2, 3]. Even with optimal treatment, patients with NMIBC are at high risk of tumor recurrence or progression to more advanced disease [3]. Recurrent NMIBC represents a heterogenous disease mix with a wide spectrum of risk for additional recurrence and progression, which have been used for patient stratification into three risk groups [4]. Patients with recurrent NMIBC of intermediate-risk can be treated with intravesical chemotherapy and /or Bacillus Calmette-Guerin (BCG) before surgical cystectomy. The second-line therapies, such as BCG plus interferon alfa-2b, valrubicin, docetaxel or gemcitabine have demonstrated modest activity in early-phase of clinical studies; and novel approaches are being studied in an effort to improve the prognosis in the high-risk clinical setting.

1.2 Intravesical BCG Immunotherapy for NMIBC

BCG for intravesical use is a live attenuated form of Mycobacterium bovis and has been approved by the Food and Drug Administration (FDA) of the United States for the treatment and prophylaxis of carcinoma in situ (CIS) of the urinary bladder, and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection (TUR) (https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM163039.pdf). Per the American Urological Association (AUA) bladder cancer guidelines it is the standard treatment for patients with high-risk NMIBC following a restaging transurethral resection of bladder tumor. Patients with NMIBC have high recurrence rate after intravesical BCG with or without chemotherapy. Standard definitions of post-BCG states may be used to guide clinical decision-making and clinical trial design [5].

BCG failure: Patients with either intermediate- or high-risk NMIBC who received induction intravesical BCG but failure to achieve tumor response. Up to 40% of patients with NMIBC will fail intravesical BCG therapy [6].

BCG unresponsive: Patients have persistent or recurrent high-grade Ta/Tis or T1 bladder cancer after completion of at least induction (≥5 doses) and one round of maintenance (or second induction; ≥2 doses) intravesical BCG; or tumor recurrent within six months after initial response. Up to 50% patients with NMIBC have tumor progression after the third cycle intravesical BCG therapy [7].

The difficulty with management of NMIBC has resulted in many attempts to improve treatment. For patients with Ta disease, without additional treatment, cancer recurrence occurs in more than 60% and disease progression occurs in more than 20%. Patients with T1 disease may experience recurrence in more than 75% of patients with progression in 35% of patients. Intravesical chemotherapy may delay recurrence, but does not prevent progression. BCG has been shown to reduce disease progression and recurrence while improving survival. The most benefit from BCG is obtained with a complete maintenance course. Response rates can improve from nearly 40% to over 70% [8, 9]. However, very few patients can tolerate a complete full course of maintenance BCG (~16%) [9]. Patients with persistent tumor or post-BCG recurrence may respond to another challenge with intravesical BCG [10]. However,

a repeat induction of BCG for patients with disease refractory to the first BCG induction only has a response rate of around 20%. Cystectomy is offered to patients who have high risk NMIBC and those who may be resistant to BCG. However, few patients want to undergo such a radical surgery. Improvements in BCG treatment, particularly the addition of systemic immunotherapy may lead to improved response rates, decreased rates of recurrence and better survival without the need for cystectomy.

Patients undergoing BCG therapy must be able to tolerate induction therapy. For any strategy to improve the anti-cancer efficacy of intravesical BCG completion of induction therapy is required. This study includes a safety lead-in to ensure patients tolerate the combination therapy of full dose BCG and a novel weekly dosing of avelumab. BCG has been shown to be effective in split dosing. If patients are not tolerant of full dose BCG, reduced dosing will be evaluated. For this study to proceed, patients must be able to tolerate induction therapy as commonly defined as receiving at least 5 of 6 weekly treatments within an 8 week period. The completion of a full induction course within eight weeks of starting treatment is the primary endpoint of this study. Patients who cannot tolerate 5 of 6 weekly treatments as part of induction therapy will be considered treatment failures.

The response to treatment at the 6 month mark has been shown to be predictive of further tumor recurrence [11]. A secondary endpoint of this study will be the rate of completion of the 6 month maintenance course which will simultaneously evaluate for tolerance of therapy at 6 months and disease response. This measure will provide a clinically meaningful endpoint of both safety and efficacy.

Recently Merck, the only source of BCG within the United States, announced a global shortage of BCG supply. This shortage may continue for the duration of this study. Recently the American Urological Association (AUA) along with several other groups including the Bladder Cancer Advocacy Network (BCAN) and the Society of Urologic Oncology (SUO) provided clinicians with recommended strategies to ensure adequate BCG supplies. This includes a recommendation that patients undergoing maintenance therapy receive a split 1/3 dose of treatment. In this study, during the time of BCG shortage, patients will be treated with the recommended split dose therapy. This will ensure that patients have responded to the initial induction therapy prior to receiving the split dose maintenance therapy.

1.2.1 Clinical safety of Intravesical BCG

The common adverse events of intravesical BCG included (≥10%):

1. Dysuria (~ 60%), irritable bladder (~ 60%), urinary frequency (40% to ≤50%), urinary urgency (6% to ≤50%), hematuria (26% to 39%), cystitis (6% to 30%), urinary tract infection (2% to 18%);
2. Malaise (≤40%), chills (9% to 34%), pain (≤17%);
3. Flu-like symptoms (24% to 33%), Fever (17% to 38%);
4. Nausea (≤16%), vomiting (≤16%), anorexia (≤11%)

1.3 PD-L1 Inhibitor on Cancer Therapy

The pathway of programmed cell death 1 receptor and its ligands (PD-1/PD-L1) in cancer is implicated in tumor escaping immune destruction and is a promising therapeutic target [12-14]. The PD-1/PD-L1 inhibitors have shown promising anti-cancer responses in a variety of cancers and the toxicities were generally manageable [15-18]. The Food and Drug Administration (FDA) has approved five immunotherapy agents for the treatment of metastatic bladder cancer. Nivolumab and pembrolizumab

target PD-1 while avelumab, atezolizumab, and durvalumab are PD-L1 inhibitors. Both pembrolizumab and atezolizumab have been approved for use in patients who are not eligible for platinum-containing chemotherapy. All five agents have approval for second line therapy following treatment with a cisplatin based regiment. A recent phase III study observed objective responses of PD-1/PD-L1 inhibitors among patients with PD-L1–negative cancers, although patients with positive PD-L1 expression may get more benefit [19]. The results indicated additional mechanisms involved in the anti-cancer efficacy of PD-L1 inhibitor.

In bladder cancer, expression of PD-L1 has been associated with poor prognosis [20]. Immunotherapy with antibodies targeting PD-1 or PD-L1 has shown significant clinical activity in patients with metastatic urothelial carcinoma [21-24]. Atezolizumab, pembrolizumab and avelumab continue to be tested in clinical studies, using systemic administration, for urothelial carcinoma including non-muscle invasive bladder cancer.

1.4 Summary of Avelumab

Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody targeting PD-L1 protein, with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, avelumab binds to PD-L1 and prevents the interaction of PD-L1 with its receptor programmed cell death protein 1 (PD-1). This inhibits the activation of PD-1 and its downstream signaling pathways. This may restore and increase immune function through the activation of cytotoxic T lymphocytes (CTLs) targeted to PD-L1-overexpressing tumor cells. In addition, avelumab induces an antibody-dependent cellular cytotoxic (ADCC) response against PD-L1-expressing tumor cells [25].

1.4.1 Pre-clinical experience with Avelumab

Pre-clinical studies by in vitro cell culture demonstrated the ADCC activity of avelumab on various human tumor cells: 1) avelumab could lyse a range of human tumor cells in the presence of Peripheral blood monocytes (PBMC) or nature killer cells (NK); 2) IFNγ and IL12 can enhance avelumab-mediated ADCC tumor cell lysis; 3) similar levels of avelumab-mediated ADCC lysis of tumor cells are seen using purified NK as effectors from either healthy donors or cancer patients [25]. Similar results were reported by Khanna et al showing that the primary mesothelioma cell lines were susceptible to avelumab-mediated ADCC in the presence of autologous natural killer cells [26].

Pre-clinical studies in murine model carrying orthotopic bladder cancer (MB49 cells) observed the antitumor effects of avelumab on non-muscle invasive bladder cancer and nonmetastatic urothelial carcinomas [27]. MB49(luc) bladder tumors are highly positive for the expression of PD-L1, and systemic immunotherapy with avelumab induced significant ($P < 0.05$) antitumor effects. These antitumor effects were more dependent on the presence of CD4 than CD8 T cells, as determined by in vivo immune cell depletions. The results from this bladder tumor model has provided the rationale for subsequent clinical studies to further identify host antitumor immune mechanisms and evaluate combinations of immune-based therapies for patients with non-muscle invasive, nonmetastatic urothelial carcinoma [27]

1.4.2 Clinical experience with Avelumab

The available clinical safety data of avelumab on approximately 1738 subjects treated with 10 mg/kg avelumab Q2W in clinical Trials is summarized in the Avelumab IB. Most of the observed AEs were either in line with those expected in subjects with advanced solid tumors or with class effects of MoAb

blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks of avelumab.

NCT02155647: In this multicenter, open-label, phase 2 trial, 88 patients with stage IV chemotherapy-refractory Merkel cell carcinoma (aged ≥18 years) were enrolled and received at least one dose of avelumab given intravenously at a dose of 10 mg/kg every 2 weeks [28]. Patients were followed up for a median of 10.4 months. The proportion of patients who achieved an objective response was 28 of 88 patients (31.8%), including eight complete responses and 20 partial responses. Responses were ongoing in 23 (82%) of 28 patients at the time of analysis. Five grade 3 treatment-related adverse events occurred in four (5%) patients: lymphopenia in two patients, blood creatine phosphokinase increase in one patient, aminotransferase increase in one patient, and blood cholesterol increase in one patient; there were no treatment-related grade 4 adverse events or treatment-related deaths. Serious treatment-related adverse events were reported in five patients (6%): enterocolitis, infusion-related reaction, aminotransferases increased, chondrocalcinosis, synovitis, and interstitial nephritis (n=1 each). Investigators concluded that avelumab was associated with durable responses and was well tolerated; therefore, avelumab represents a new therapeutic option for patients with advanced Merkel cell carcinoma [28].

NCT01772004: The phase 1a, dose-escalation trial assessed four doses of avelumab (1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg), with dose-level cohort expansions to provide additional safety, pharmacokinetics, and target occupancy data [29]. Fifty-three patients were enrolled including four patients at 1 mg/kg, 13 at 3 mg/kg, 15 at 10 mg/kg, and 21 at 20 mg/kg. Among 18 patients analyzed in the dose-limiting toxicity analysis set, only one dose-limiting toxicity occurred, at the 20 mg/kg dose, and thus the maximum tolerated dose was not reached. In all 53 enrolled patients, common treatment-related adverse events (occurring in >10% of patients) included fatigue (21 patients [40%]), influenza-like symptoms (11 [21%]), fever (8 [15%]), and chills (6 [11%]). Grade 3-4 treatment-related adverse events occurred in nine (17%) of 53 patients, with autoimmune disorder (n=3), increased blood creatine phosphokinase (n=2), and increased aspartate aminotransferase (n=2) each occurring in more than one patient (autoimmune disorder in two patients at 10 mg/kg and one patient at 20 mg/kg, increased blood creatine phosphokinase in two patients at 20 mg/kg, and increased aspartate aminotransferase in one patient at 1 mg/kg, and one patient at 10 mg/kg). Six (11%) of 53 patients had a serious treatment-related adverse event: autoimmune disorder (two [13%]), lower abdominal pain (one [7%]), fatigue (one [7%]), and influenza-like illness (one [7%]) in three patients treated at 10 mg/kg dose level, and autoimmune disorder (one [5%]), increased amylase (one [5%]), myositis (one [5%]), and dysphonia (one [5%]) in three patients who received the 20 mg/kg dose. The clinical activity were observed in various solid tumors, with partial confirmed or unconfirmed responses in four (8%) of 53 patients; 30 (57%) additional patients had stable disease. Pharmacokinetic analysis (n=86) showed a dose-proportional exposure between doses of 3 mg/kg and 20 mg/kg and a half-life of 95-99 h (3·9-4·1 days) at the 10 mg/kg and 20 mg/kg doses. Target occupancy was greater than 90% at doses of 3 mg/kg and 10 mg/kg. Antidrug antibodies were detected in two (4%) of 53 patients. No substantial differences were found in absolute lymphocyte count or multiple immune cell subsets, including those expressing PD-L1, after treatment with avelumab [29].

In the multi-center phase Ib dose expansion cohort, investigators assessed the safety and antitumor activity of avelumab in patients with refractory metastatic urothelial carcinoma [24]. Patients with urothelial carcinoma progressing after platinum-based chemotherapy and unselected for PD-L1 expression received

avelumab 10 mg/kg intravenously every 2 weeks. Forty-four patients were treated with avelumab and followed for a median of 16.5 months. The most frequent treatment-related adverse events of any grade were fatigue/asthenia (31.8%), infusion-related reaction (20.5%), and nausea (11.4%). Grades 3 to 4 treatment-related adverse events occurred in three patients (6.8%) and included asthenia, AST elevation, creatine phosphokinase elevation, and decreased appetite. The confirmed objective response rate by independent central review was 18.2%, including five complete responses and three partial responses. Seven of eight responding patients had PD-L1-positive tumors. The median progression-free survival was 11.6 weeks; the median overall survival (OS) was 13.7 months, with a 12-month OS rate of 54.3% (95% CI, 37.9% to 68.1%). The results indicated that avelumab was well tolerated and associated with durable responses and prolonged survival in patients with refractory metastatic urothelial carcinoma [24].

1.5 Rationale for this Study

Patients with NMIBC are at high risk of tumor recurrence or progression to more advanced disease. BCG is the standard of care for intravesical therapy for CIS and non-muscle invasive urothelial carcinoma. Unfortunately, the tumor response to BCG-based immunotherapy is heterogeneous. Potential treatment failures may be due to inhibitory immune receptors and their ligands like PD-1/PD-L1. The overall prognosis for many patients with NMIBC is poor with radical cystectomy as an alternative treatment and this disease carries a high unmet medical need. Avelumab is a fully human IgG1 MAb targeting PD-L1, which differs from other checkpoint-blocking antibodies in its ability to mediate antibody-dependent cell-mediated cytotoxicity. Pre-clinical studies in murine model carrying bladder cancer (MB49 cells) demonstrated the antitumor effects of avelumab on non-muscle invasive bladder cancer and nonmetastatic urothelial carcinomas [27]. The antitumor effects were more dependent on the presence of CD4 than CD8 T cells; combination treatment of avelumab and intravesical BCG could increase numbers of CD4 and CD8 T cells within the tumor mass [27]. Clinical studies found that avelumab was well tolerated and associated with durable responses and prolonged survival in patients with refractory metastatic urothelial carcinoma [24]. We hypothesize that systemic immunotherapy with avelumab combined with BCG intravesical therapy may increase tumor response, reduce tumor recurrence, and prolong disease-free survival in patients with NMIBC.

1.5.1 Rationale for potential dose de-escalation

As described in section 1.2.1, there are concerns related to adverse events of intravesical BCG, including bladder irritation /infection and systemic BCG reactions such as fever and flu-like symptoms. These symptoms may prevent a patient from receiving a full induction course of BCG, as defined as at least 5 of 6 weekly instillations of BCG. Patients who cannot tolerate a full course of BCG are considered BCG intolerant. The addition of immune checkpoint inhibitors to BCG therapy may result in an increase of BCG intolerance and prevent patients from receiving a full induction course of BCG. To evaluate the safety and feasibility of intravesical BCG in combination with avelumab and to ensure patients tolerate a complete induction course of BCG (at least 5 of 6 instillations), a safety lead-in will be conducted prior to dose expansion study.

1.5.2 Rationale for correlative study

Previous studies reported that large amounts of functional T-cells could be detected in urine of patients with NMIBC who were treated with weekly intravesical BCG [30]. Pre-clinical studies in mice model

showed that avelumab monotherapy was highly effective in reducing the growth of bladder tumors in immune intact mice; combination of avelumab and intravesical BCG could increase numbers of CD4 and CD8 T cells within the bladder tumor mass [27]. Moreover, flow cytometry can be used to identify cellular immune reaction in urine of patients with superficial bladder cancer after intravesical BCG treatment [31]. In this study, immune function in blood and immune response in urine will be evaluated by a multiplexed immunoassay to identify potential biomarkers for immune response that may predict response to therapy.

2 STUDY OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, feasibility and preliminary anti-tumor activity of a novel weekly dosing of avelumab in combination with standard intravesical Bacille Calmette-Guérin (BCG) in patients with NMIBC who are eligible for induction BCG**.**

2.1 Objectives

2.1.1 Primary Objective

- To evaluate the safety and tolerability of combination induction therapy with BCG + avelumab as defined as the ability to complete a full induction course (at least 5 of 6 treatments of BCG + avelumab within eight weeks of starting treatment).

2.1.2 Secondary Objectives

- To evaluate the feasibility and tolerability of combination therapy with BCG + avelumab as measured by the endpoint of 6 month treatment completion rate based on patients completion of at least 2 of 3 treatments within a 5 week period at the 6 Month maintenance treatment.
- To evaluate 3-month complete response (CR) rate, 6-month CR rate, recurrence free survival (RFS), cystectomy-free survival (CFS), and overall survival.

2.1.3 Patient-reported Outcome Objective

- To evaluate impact of combination therapy with BCG + avelumab on quality of life in patients with NMIBC.

2.1.4 Exploratory Objective

- To identify potential biomarkers that would associate with tumor response from the combination of avelumab and intravesical BCG.

2.2 Study Endpoints

2.2.1 Primary endpoints

- Completion of induction therapy with combined BCG + avelumab as defined as freedom from unacceptable toxicities preventing completion of at least 5 of 6 treatments of BCG + avelumab within 8 weeks.

2.2.2 Secondary Endpoints

- 6 Month maintenance treatment completion as defined as completion of at least 2 of 3 maintenance treatments within a 5-week period without unacceptable toxicities or disease progression. Disease status will be evaluated based on cystoscopy and urine cytology prior to maintenance therapy.

Patients with persistent or recurrent high-grade disease at 6 Month cystoscopy will be taken off treatment. Low-grade recurrence will be tolerated without treatment interruption.

- 3-month and 6-month complete response (CR) based on negative cystoscopy and urine cytology.
- Recurrence free survival (RFS) at 6 and 12 months, defined as proportion of patients who are alive and free of persistent or recurrent NMIBC based on cystoscopy, cytology and/or biopsy.
- Progression-free survival (PFS) at 6 and 12 months, as defined by time from day of first treatment to first progression to higher grade or stage, including muscle-invasive disease or death from any cause
- Cystectomy-free survival (CFS), defined as time from study initiation to cystectomy or death
- Overall survival, defined as time from day of first treatment to death from any cause

2.2.3 Exploratory endpoints

- To obtain preliminary data of potential biomarkers that would associate with tumor response from the combination of avelumab and intravesical BCG.
- Avelumab combined with intravesical BCG will improve quality of life in patients with NMIBC.

3 STUDY POPULATION

Target population: Male or female patients must be 18 years of age or older before the screening visit to be enrolled in the study. Patients must have histologic or cytological diagnosis of Non-muscle Invasive Bladder Cancer (NMIBC), and the cancer is BCG-treated but unresponsive (recurrent or persistent). Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate clinical laboratory values.

The following eligibility criteria are designed to select patients; all relevant medical and nonmedical conditions should be taken into consideration to decide if a particular patient is suitable for this protocol

3.1 Inclusion Criteria

1. Histologically or cytologically documented Non-muscle Invasive Bladder Cancer (NMIBC).
2. Patient with BCG-treated but unresponsive NMIBC (persistent or recurrent defined as tumor lesion present after prior response).
3. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 2.
4. Patients who are able to understand and sign the informed consent form.
5. Age ≥ 18 years old
6. Ability to comply with protocol
7. Life expectancy >/=12 weeks
8. Adequate hematologic and end-organ function
    - ANC ≥ 1500/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first dose of study treatment)
    - Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first dose of study treatment)
    - Hemoglobin ≥ 9.0 g/dL; Patients may be transfused or receive erythropoietic treatment, at least 7 days prior to the first dose of study treatment, to meet this criterion.

- AST and ALT ≤ 2.5 × ULN.
- Serum bilirubin ≤ 1.5 × ULN; Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
- INR and aPTT ≤ 1.5 × ULN; this applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
- Creatinine clearance >/=30 milliliters per minute (mL/min) (calculated using the Cockcroft-Gault formula)

9. For women of childbearing potential: Negative serum or urine pregnancy test at screening.
10. For both male and female subjects: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 30 days after the last dose of study drug

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

1. Evidence of locally advanced or metastatic bladder cancer (including current disease involving renal pelvis, ureter, or prostatic urethra).
2. Evidence of muscle-invasive bladder cancer
3. Evidence of extravesical bladder cancer
4. Active central nervous system (CNS) metastases.
5. Prior treatment with PD-L1 or PD-1 inhibitor.
6. Prior radiation to bladder
7. Patient has a known additional malignancy that required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin.
8. Patient is considered a poor medical risk that would interfere with cooperation with the requirements of the study.
9. Patient has a condition or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
10. Patient has not recovered (i.e, to ≤Grade 1 or to baseline) from previous intravesical BCG or other anti-cancer therapy induced AEs.
    - alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable
11. Treatment with any approved anti-cancer therapy, including chemotherapy (systemic or intravesical), radiation therapy, or hormonal therapy within 3 weeks prior to the first dose of study treatment
    - Use of hormone-replacement therapy and oral contraceptives is permitted.
12. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 4 weeks prior to the first dose of study treatment
13. Pregnant or lactating, or intending to become pregnant during the study
    - Women who are not postmenopausal (≥ 12 months of non−therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to the first dose of study treatment.

14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
15. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells
16. Allergy or hypersensitivity to components of the avelumab formulation
17. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
    - Patients with medically controlled endocrinopathy (e.g., hypothyroidism, adrenal insufficiency), diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible
18. Prior allogeneic stem cell or solid organ transplantation
19. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
20. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
21. Positive test for HIV
22. Active hepatitis B (positive hepatitis B surface antigen [HBsAg] test at screening);
    - Patients with past or resolved hepatitis B (HBV) infection (positive anti-hepatitis B core antigen [anti-HBc] antibody test) are eligible. HBV DNA must be obtained in these patients prior to the first dose of study treatment.
23. Active hepatitis C
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction assay is negative for HCV RNA.
24. Active infection requiring systemic therapy
25. Severe infections within 4 weeks prior to the first dose of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
26. Significant cardiovascular disease, such as cerebral vascular accident/stroke (< 6 months prior to enrollment), New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina
27. Administration of a live/attenuated vaccine within 4 weeks prior to the first dose of study treatment, within 5 months following the administration of the last dose of study drug, or anticipation that such a live/attenuated vaccine will be required during the study
28. 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.

4 PATIENTS REGISTRATION

4.1 Required Protocol Specific Regulatory Documents

This protocol, the Informed Consent document, any information to be given to the patient, and relevant supporting information must be submitted to the IRB by the Principal Investigator and reviewed and approved by the IRB before the study is initiated.

4.2 Patients Registration and Enrollment

Patients must have signed and dated all applicable consents and authorization forms to be registered in the Velos eResearch database system, which is sponsored by The University of Oklahoma Stephenson Cancer Center (OU-SCC).

A Screening identification (Screening ID) number will be provided by OU-SCC research staff. After all screening procedures and assessments have been completed and eligibility has been established, the subject Study ID number will be generated by OU-SCC. Once the patient has been provided a Study ID number, only the Study ID number should be used. Both patient ID numbers should be documented in Velos.

Patients must not start protocol treatment prior to registration and enrollment. A patient will start protocol treatment only after the pre-treatment evaluation is complete and eligibility criteria have been met.

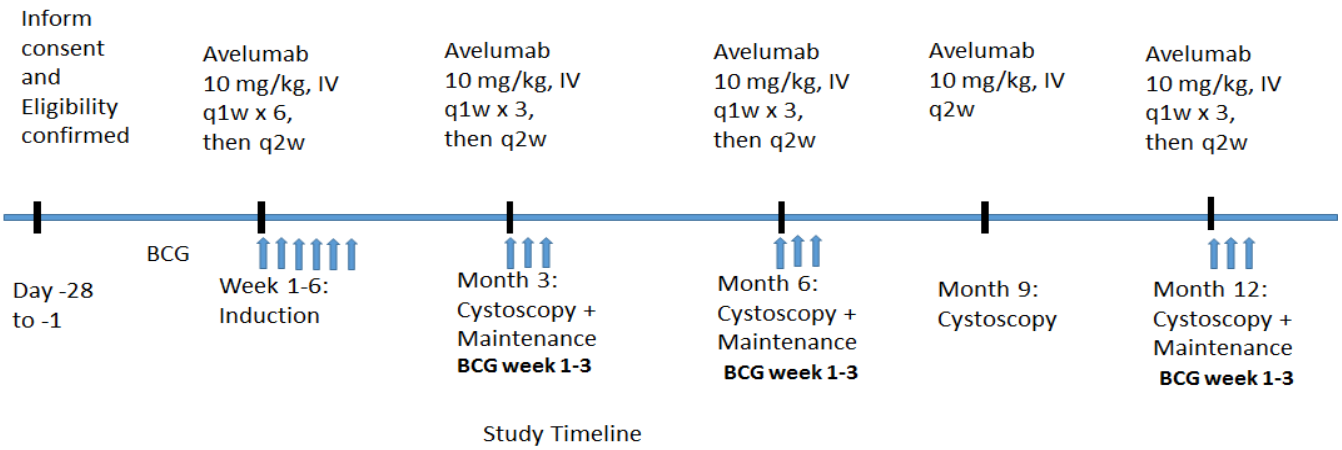
NOTE: Per the Institutional Review Board (IRB) reporting, a patient is considered accrued once he or she signs a consent form for the study. A patient is considered enrolled once the patient begins treatment. Evaluable patients are defined in protocol Section 8.2.1.

5 STUDY DESIGN

5.1 Study Timeline

Study timeline is summarized in Figure 1 Schema.

Figure 1 Schema



5.2 Overall Study Design

This is an open-label phase Ib trial of avelumab and intravesical BCG in patients with NMIBC. The study will utilize a modified 3+3 design for potential dose de-escalation in case of patients cannot tolerate to a full dose intravesical BCG. In order to adequately assess safety data at the conclusion of this combination therapy, 3~6 patients will be enrolled at starting dose level (dose level 1). Dose limiting toxicity will be based on the first 6 weeks of proposed study treatment. If 0/3 patients experience a DLT, dose expansion cohort will be activated for additional 15 patients. If 1/3 patients experiences a DLT, the dose level 1 will be expanded to 3 more patients. If 1/6 patients experiences a DLT, the dose expansion cohort will be activated for additional 12 patients. If 2 or more of the 6 patients experience a DLT, the dose level -1 will be evaluated.

At the dose level 1, 3~6 patients will be enrolled to evaluate the safety of proposed combination therapy with standard BCG dosing (50 mg) plus avelumab (10 mg/kg, IV weekly during BCG and every two weeks between BCG). The ability of patients to receive a complete induction course of combination therapy is defined as 5 of 6 weekly treatments of BCG with weekly infusion of avelumab within an 8 week period. Patients will continue maintenance therapy if they tolerate the induction course. Eligible patients will receive avelumab 10 mg/kg, IV weekly dosing plus intravesical BCG 50 mg weekly, 6 weeks on, then 6 weeks off during induction and will continue on a standard maintenance regimen with combination therapy for 1 year. Maintenance therapy beyond 1 year will be at the discretion of the treating physician and will be BCG monotherapy.

The dose limiting toxicity (DLT) period is weeks 1-6 (42 days). If the combination therapy in dose level 1 is well tolerated (0/3 or 1/6 patients experience a DLT), additional 12~15 patients with the same eligibility criteria will be enrolled at dose level 1 for a total of 18 patients in a dose expansion study. If the combination therapy in dose level 1 is not tolerated (2 or more patients experience a DLT), dose level -1 (avelumab 10mg/kg and BCG 33mg) will be evaluated in 3~6 eligible patients. If the combination therapy in dose level -1 is well tolerated (0/3 or 1/6 patients experience a DLT), additional 12~15 patients with the same eligibility criteria will be enrolled at dose level -1 for a dose expansion study. If the combination therapy in Cohort -1 is not tolerated (2 or more patients experience a DLT), the study will be suspended for reassessment.

5.2.1 Definition of Dose limiting toxicity

During safety lead-in phase, Dose limiting toxicity (DLT) will be monitored during the first 6 weeks of the combination avelumab and intravesical BCG. DLTs will be defined as any and all adverse events at least possibly related to study drug which occur in the DLT evaluation period and meet the criteria below, as evaluated by the NCI-CTCAE version 5.0.

Note: DLTs and other toxicities will be discussed between the Principal Investigator, and the Data Safety Monitoring Committee (DSMC). The discussions are the basis for the decisions regarding dose expansion (or de-escalation) according to the rules of the protocol.

DLT will be classified as either hematologic or non-hematologic toxicity (assessed in accordance with the CTCAE Version 5.0 criteria).

The following are DLTs:

1. Toxicity causing greater than 2 weeks of dose delay. For example, if a subject has dose delay greater than 2 weeks due to an AE, such AE is a DLT.
2. Grade 4 neutropenia greater than 5 days.
3. ALT/AST > 3x ULN with bilirubin > 2x ULN without another explanation (e.g., cholestasis)
4. Any Grade 3 hypersensitivity reaction is a DLT
5. Grade 4 thrombocytopenia of any duration
6. Grade 3 thrombocytopenia with significant hemorrhage of any duration
7. Febrile neutropenia

And, any non-hematological Grade ≥ 3 toxicities will be a DLT.

The following may be considered as exceptions to DLTs:

1. Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours
2. Grade 3 fatigue lasting < 5 days
3. Grade 3 hypertension that can be controlled with medical therapy
4. An increase of indirect (unconjugated) bilirubin indicative of Gilbert's syndrome
5. Serum lipase and/or serum amylase CTCAE Grade 3 ≤ 7 consecutive days without clinical signs or symptoms of pancreatitis

5.2.1.1 Definition of DLT Evaluable Population:

Patients enrolled in safety lead-in cohort who receive at least 4 doses and complete the DLT observation period (the first 42 days of induction treatment), unless the patient discontinued the study treatment due to a DLT.

5.3 Rationale for Avelumab Dose and Schedule

In this clinical trial, the avelumab dose will be 10 mg/kg administered as 1-hour IV infusions, once every week during BCG and once every two weeks between BCG. Avelumab IV 10 mg/kg Q2W is the recommended dosing regimen and has been administered to a total of 1738 patients in dose expansion phase of the Study EMR100070-001 (see BAVENCIO® (avelumab) U.S. Package Insert and avelumab IB for details). One additional dose regimen, 10 mg/kg once a week for 12 weeks followed by 10 mg/kg once every 2 weeks, is also being investigated in patients with non-small cell lung cancer (NSCLC). Preliminary data from the 1L NSCLC cohort of EMR100070-001 showed that approximately 80% of reported responses occurred within 12 weeks of treatment initiation, and the majority of responses appeared to be durable. It is not expected that the exposure at 10 mg/kg once every week would substantially impact the manageable safety profile currently observed with 10 mg/kg once every 2 weeks dosing (See avelumab IB for details).

5.4 Rationale for Avelumab and Intravesical BCG combination

See section 1.5.

6 TREATMENT PLAN

6.1 Treatment Dose and Schedule

Patients enrolled in this study will receive combination treatment of IV avelumab and intravesical BCG. The dose level and patient number in each cohort are summarized in Table 1.

Table 1 Dose levels for safety lead-in and expansion cohorts

Dose Level	Number of Patients	Avelumab	Intravesical BCG
-1 (reduced dose)	6	10 mg/kg, IV, once a week, during BCG. 10mg/kg, IV, every other week between BCG	**Induction (cycle 1)**: BCG 33 mg, intravesical, weekly x 6 doses (weeks 1-6); **Maintenance (Month 3, 6, 12)**: BCG 33 mg, intravesical, weekly x 3 doses.
1 (starting dose)	6-	10 mg/kg, IV, once a week, during BCG. 10mg/kg, IV, every other week between BCG	**Induction (cycle 1)**: BCG 50 mg, intravesical, weekly x 6 doses (weeks 1-6); **Maintenance (Month 3, 6, 12)**: BCG 50 mg, intravesical, weekly x 3 doses.*
Final dose	12 (total of 18 patients at final dose)	10 mg/kg, IV, once a week, during BCG. 10mg/kg, IV, every other week between BCG	**Induction (cycle 1)**: BCG 50 mg (or 33 mg), intravesical, weekly x 6 doses; **Maintenance (Month 3, 6, 12):** BCG 50 mg (or 33 mg), intravesical, weekly x 3 doses.
One cycle=12 weeks (84 days). ***During periods of BCG shortage, split dose maintenance therapy (1/2-1/3) can be used at the PI discretion until sufficient BCG supplies are obtained.**			

Dose interruption may be allowed for up to 3 weeks (21 days) for intra-vesical-BCG or 12 weeks for avelumab treatment related grade 3-4 adverse events.

Cystoscopy will be performed at screening, and in months 3, 6, 9 and 12 as standard of cancer care (SOC).

6.2 Drug Formulation, Packaging and Handling

6.2.1 Avelumab

Avelumab will be supplied by EMD Serono, Inc. Drug supplies will be shipped in transport cool containers (2°C to 8°C) to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain

appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

Avelumab is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1. Avelumab drug product is a sterile, clear, and colorless concentrate solution intended for IV administration. It is presented at a concentration of 20 mg/mL with a nominal volume of 10 mL in glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal. Each vial is intended for single-use only and contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20.

Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long-term stability studies with avelumab.

6.2.2 Bacille Calmette-Guérin

BCG for intravesical use is an attenuated, live culture preparation of the BCG strain of *Mycobacterium bovis*. BCG is commercially available and will be paid for by patients' medical insurance (https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM163039.pdf). The freeze-dried BCG preparation is delivered in glass vials, each containing 1 to 8 × 10^8 CFU of BCG, which is equivalent to approximately 50 mg wet weight. No preservatives have been added. For detailed information on the formulation and handling of BCG, refer to BCG package insert.

6.3 Drug Preparation and Administration

Informed consent must be signed and all eligibility criteria must be met and documented before protocol therapy administration. The protocol therapy will be administered only to eligible subjects under the supervision of the Investigator or identified Sub-investigator(s).

6.3.1 Avelumab

Avelumab will be administered by IV 10 mg/kg over approximately 1 hour at the following schedule:

Induction phase:

- once weekly while receiving BCG treatment
- once every 2 weeks after BCG treatment is completed

Maintenance phase:

- Once weekly during BCG
- Once every 2 weeks after completion of BCG

One cycle = 12 weeks (84 days). A standard maintenance therapy regimen will be provided with BCG occurring at Month 3, 6, and 12. Avelumab treatment ends at the conclusion of Month 12 maintenance therapy. In both the induction and maintenance phases, no avelumab will be administered the week following BCG therapy completion. The subsequent every two week avelumab dosing will begin following this one week period.

For administration in clinical trials, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively, a 0.45% saline solution can be used if needed. The verified avelumab concentration range in the infusion solution is 0.016 mg/mL to 8 mg/mL.

The investigator and team should make every effort to target infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of -10 minutes and +20 minutes are permitted (i.e., 50−80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs.

In case prepared dosing solution cannot be administered immediately after preparation, the acceptable holding time is: no more than 4 hours at room temperature (15-25°C, 59-77°F), including infusion time, or no more than 24 hours under refrigerated conditions (2-8°C, 36-46°F), including infusion time.

If stored under refrigerated conditions, allow each bag to equilibrate to room temperature (15-25°C, 59-77°F), preferably for one hour before administration.

Premedication with an antihistamine and with acetaminophen (for example, 25 – 50 mg diphenhydramine and 500 – 650 mg acetaminophen IV or oral equivalent) approximately 30 to 60 minutes before each dose of avelumab is mandatory. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

During the treatment between BCG, avelumab may be administered up to 2 days before or after each scheduled treatment day for administrative reasons, except for day 1 of BCG induction phase and C1D1 of BCG maintenance phase.

6.3.1.1 Special Precautions for Avelumab Administration

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. 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.

In order to mitigate infusion-related reactions, patients have to 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 based upon clinical judgment and presence/severity of prior infusion reactions. Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions.

Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. If an infusion/allergic reaction occurs, the patient must be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately.

6.3.2 Intravesical BCG

During BCG Induction Course (12 weeks), patients will receive BCG at the assigned dose weekly for a total of six doses. During the BCG Maintenance Course, patients receive BCG at the assigned dose weekly for a total of three doses per cycle at Months 3, 6, and 12. Patients with persistent disease at the Month 3 cystoscopy can undergo an additional repeat induction course of BCG + avelumab, providing no disease progression. Primary outcome remains completion of maintenance at 6 Month from trial initiation.

Induction phase (cycle 1):

- Once weekly for up to six doses

Maintenance phase (Month 3, 6, and 12):

- Once weekly for 3 doses per cycle

Locally sourced commercial stock of BCG should be used. A single dose consists of one reconstituted vial. For intravesical use, the entire vial is reconstituted with sterile saline. BCG is viable upon reconstitution. Refer to the package insert for detailed preparation instructions and stability data. During times of BCG shortage, split dose maintenance therapy (1/2-1/3) will be permitted at PI discretion.

Patients should minimize fluid intake before treatment with BCG. Additionally, complete bladder drainage should occur via catheter drainage placed immediately prior to BCG administration. Premedication for BCG therapy to ensure adequate instillation is acceptable.

Instill BCG (intravesical) by gravity; retain for as long as possible, according to local treatment protocols. Following bladder instillation, patients should be instructed to void in a seated position in order to avoid the splashing of urine; burning may occur with the first void following therapy. Prior to flushing, disinfect the urine for 15 minutes with an equal amount of household bleach (this should be done for the first 6 hours after therapy). After administration, patients should drink plenty of water in order to flush the bladder.

6.4 Dose Modification or Discontinuation

Study treatment dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (eg, surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption for intravesical-BCG or 12 weeks for avelumab, unless otherwise discussed with the Principal Investigator.

Toxicity and grades will be classified using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). Safety plan for this study is described in sections 6.4.1, 6.4.2, and section 9.

Interruption of intravesical-BCG does not preclude continuation of avelumab and vice versa. For instance, if an AE is attributed to intravesical-BCG during the study treatment, then avelumab will be continued while the BCG held. While BCG is held, the patient will continue to receive avelumab, be monitored for safety, and will resume intravesical-BCG within 3 weeks if the toxicity resolves. If the AE is immune related and attributed to avelumab; then BCG will be continued while the avelumab is held.

In case treatment interruption for one of the investigational drugs (avelumab or BCG) is required for drug-related toxicity, the dose of the other drug may also be interrupted based on the guidance provided for toxicity management, product labeling, and institutional guidelines according to investigator's best medical judgement.

Note: If the patient does not receive 5 doses of scheduled 6 doses of BCG within eight weeks at the time of induction, then the patient is considered treatment failure.

6.4.1 Avelumab Dose Interruption and Toxicity Management

There will be no dose reduction for avelumab in this study. Every effort should be made to administer the investigational products at the planned dose and schedule, but the next infusion may be omitted or delayed based on treatment related toxicity.

Avelumab treatment may be delayed in the event of significant toxicity that is considered related to the study treatment. In the event of multiple toxicities, dose delays should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom. In addition to dose delays, investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below. Avelumab dosing may be interrupted up to 12 weeks. Recommended avelumab treatment delays in case of avelumab drug-related toxicity are shown in Table 2,

Table ***3***, and Table 4.

Methods such as interruption to improve patient's AE symptoms at low CTCAE Grade is allowed at the Principal Investigator's discretion once the DLT period has completed.

Table 2 Dose interruption for avelumab-related toxicities

Toxicity	NCI CTCAE Grade	Avelumab dose modification
General Toxicity Management (other than infusion-related reaction/ hypersensitivity and irAEs)	Grade 1-2	Continue as per schedule.
	Grade 3	1. Withhold avelumab until recovery to Grade ≤1. 2. Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 within 12 weeks of last administration or upon recurrence of the same Grade 3 toxicity except for laboratory values out of normal range that do not have any clinical correlate.
	Grade 4	Permanently discontinue avelumab except for laboratory values out of normal range that do not have any clinical correlate.
Infusion-related Reaction	Grade 1-4	See Table ***3***
Hypersensitivity reactions	Grade 3-4	See sections 6.3.1.1 and 6.4.1.1
Immune-related AE (irAE)	Grade 1-4	See section 6.4.1.2 and Table 4

Table 3 Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modifications
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	• Stop avelumab infusion. • Resume infusion at 50% of previous rate* as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, 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 bag infusion tubing from the patient. • Avelumab treatment must be permanently discontinued.
*If avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions. In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications, the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the Investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication.	

6.4.1.1 Management of Avelumab-related Severe Hypersensitivity Reactions and Flu-like Symptoms

Many mAb therapies can induce flu-like symptoms and hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis.

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment if required. Patient should be placed on monitor immediately and epinephrine injection and dexamethasone infusion should be available for immediate access.

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable nonsteroidal anti-inflammatory drugs (NSAID) dose (eg, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered at Investigator discretion 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (eg, paracetamol or ibuprofen) and rigors (eg, meperidine) may be given to patients at the discretion of the Investigator.

6.4.1.2 Management of Avelumab Immune-Related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, avelumab may cause toxicity by increasing the immune response, leading to inflammatory reactions collectively referred to as immune-related adverse events (irAEs).

Immune-related adverse events described with this class of drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, rash, nephritis and renal dysfunction, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any AE which may have an underlying immune-mediated mechanism including those described above, and without other clear etiologies, should be considered immune-related and managed according to guidelines described in this section.

If a patient has an AE that may be considered immune mediated, treatment for the AE should be administered as if the patient is receiving avelumab.

Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade):

- Grade 1 or 2: treat symptomatically or with moderate-dose steroids, more frequent monitoring;
- Grade 1 or 2 (persistent): manage similar to high grade AE (Grade 3 to 4);
- Grade 3 or 4: treat with high-dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in Table 4.

Table 4 Management of Avelumab Immune-Related Adverse Events– to be followed only when the Adverse Event is deemed immune related

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI CTCAE v4)	**Initial management**	**Follow-up management**
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	Continue avelumab Symptomatic treatment (eg, loperamide)	Close monitoring for worsening Symptoms. Educate patient to report worsening immediately If worsens: Treat as Grade 2 or 3 or 4
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids	Withhold avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy.

indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool		If persists >5-7 days or recur: Treat as Grade 3 to 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3 1.0 to 2.0 mg/kg/day prednisone 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 following steroids taper (for initial Grade 3) If worsens, persists >3 to 5 days, orrecurs after improvement: Add infliximab 5 mg/kg (if no contraindication); Note: infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Severity of Rash (NCI-CTCAE v4)	**Initial management**	**Follow-up management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab Symptomatic therapy (eg, antihistamines, topical steroids)	If Grade 2 persists >1 to 2 weeks or recurs: Withhold avelumab Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, and resume 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 avelumab for Grade 4 or recurrent Grade 3 Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent.	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab following steroids taper (for initial Grade 3)

	Add prophylactic antibiotics for opportunistic infections	
Pulmonary AEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial management**	**Follow-up management**
Grade 1 Radiographic changes only	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 Mild to moderate new symptoms	Withhold avelumab therapy. Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone 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 following steroids taper; If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone 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 (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		

Grade of liver Function Tests Elevation (NCI-CTCAE v4)	Initial management	Follow-up management
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3x ULN	Withhold avelumab; Increase frequency of monitoring to every 3 days	If returns to Grade ≤1: Resume routine monitoring, resume avelumab therapy If elevations persist >5 to 7 days or worsens: Treat as Grade 3 to 4
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Permanently discontinue Avelumab. Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent 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 v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤1:

	1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy 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.	Once improving, taper steroids over at least 1 month.

	Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	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: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	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)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism),	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

	corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum thyroxine 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	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.

	hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**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 restarting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent	If improves to Grade ≤ 1: Taper steroids over at least 1 month

	and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections Specialty consult.	
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	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.		

6.4.2 Intravesical-BCG Dose Modification and Toxicity Management

6.4.2.1 Dose Modification

For patients enrolled in safety lead-in cohort, there will be no dose reduction for intravesical-BCG during induction treatment.

For patients enrolled in the safety lead-in cohort who do not have a DLT during induction treatment and for patients enrolled in dose expansion cohort, dose reduction is allowed for intravesical BCG at the treating physician's discretion in order to manage BCG-related toxicities (**Table 5**). For patients who are unable to tolerate full dose Intravesical BCG due to Intravesical BCG-related toxicities, dose reductions should be attempted before complete discontinuation of therapy. Initial reduction to -1 Level is suggested. Additional dose reductions to -2 Level dose can also be considered prior to complete discontinuation. If patient's symptoms improve during dose reduction, consider titrating dose back up to full dose.

Table 5 Intravesical BCG Dose levels for intra-patient dosing reduction

Full Dose	-1 Level	-2 Level
50 mg	33 mg	25 mg

Delayed Instillations

Delaying instillations of intravesical BCG is not encouraged but is allowed due to urinary tract infections, severe urinary symptoms, gross hematuria, traumatic catheterization or other circumstances at the discretion of the treating physician. Patients who postpone an instillation should resume treatment the following week. Dose and/or schedule modifications should be recorded on both source documents and CRFs.

Discontinuation of Instillations

Dose reduction should be considered before complete discontinuation of intravesical BCG instillations. Intravesical BCG should be discontinued for BCG treatment-related sepsis or extravesical (non-bladder) BCG infection.

Dwell Time

BCG administration and dwell time should follow local treatment protocols. Intravesical BCG dwell time may be up to 2 hours. Duration of retention of intravesical BCG can be shortened if medically indicated (e.g. pain or bladder spasm uncontrollable by symptomatic medications) at the treating physician's discretion as per usual standard of care. If needed, the use of an indwelling catheter during treatment, or anticholinergics, may be considered. If patient is unable to hold Intravesical BCG for 1 hour, a dose reduction should be applied.

Times of BCG Shortage

During periods of BCG shortage, split dose maintenance BCG therapy (1/2-1/3) according to institutional standard, may be used to maintain adequate BCG supply.

6.4.2.2 Toxicity management

Methods to improve patient's symptoms such as use of anticholinergics or antibiotics is allowed at the treating physician's discretion as per usual standard of care. Recommendations for management of Intravesical BCG-specific toxicities are shown in **Table 6**.

Table 6 Intravesical BCG related symptom alleviation and toxicity management

Toxicity	Recommendations
Transient symptoms: urinary frequency, urgency, dysuria, cystitis, malaise, fever < 38.5°C	Expected after intravesical BCG and usually resolves within 48 hrs. Consider symptomatic treatment (anticholinergics, pyridium, acetaminophen). Consider urine culture. Continue intravesical BCG treatment.
Persistent (> 48hr) fever < 38.5°C, cystitis, malaise	Urine culture; hold BCG until symptoms subside.
Fever > 38.5°C for 12-24 h	Urine culture; if culture is negative, consider Isoniazid 300 mg daily for 3 months; May resume intravesical BCG when asymptomatic.

Toxicity	Recommendations
Acute severe illness, local or systemic pneumonitis, hepatitis, prostatitis, ureteral obstruction, renal abscess, persisting high fever > 39°C	Isoniazid 300 mg, rifampin 600 mg and/or ethambutol 1200 mg, daily for 6 months; Discontinue intravesical BCG.
Sepsis	Isoniazid 300 mg, rifampin 600 mg and/or ethambutol 1200 mg daily for 6 months; cycloserine 500 mg twice daily orally; high-dose corticosteroids immediately; Discontinue intravesical BCG.

6.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

6.6 Treatment Duration

Patients who complete BCG induction and the Month 3 maintenance treatment without unacceptable toxicity may continue a maintenance treatment regimen up to Month 12 as per study schema. Avelumab treatment will end at the conclusion of Month 12 maintenance BCG therapy. Additional BCG maintenance monotherapy will be at the discretion of the treating physician and considered standard of care.

6.7 Treatment Discontinuation

Patients must permanently discontinue study treatment (avelumab and BCG) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of cystoscopy, radiographic and local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)
- Patients have Cystoscopy or Radiographic disease progression or symptomatic deterioration attributed to disease progression

The primary reason for study treatment discontinuation should be documented in the patient's medical records. Patients who discontinue study treatment prematurely will be replaced.

6.8 Prohibited Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than avelumab and intravesical-BCG
- Systemic glucocorticoids for any purpose other than to modulate symptoms from a suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. In such cases, systemic steroids should be stopped at least 24 hours prior to the next dose of avelumab.
- **Note**: Inhaled steroids are allowed for the management of asthma.
- Live vaccines within 14 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, and rabies and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, however, and are not allowed.
- Prophylactic cytokines (G-CSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current ASCO guidelines [32].
- Any surgery that involves tumor lesions. Note: Administration of radiation therapy or surgery done that involves tumor lesions will be considered as disease progression at the time the procedure is performed.

If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. The decision to continue the patient on study therapy, however, requires the mutual agreement of the Sponsor-Investigator and the patient.

6.9 Duration of Follow-up

The maximum follow-up period will be up to 1 year. For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression or to the date of censoring (dropout, end of study), and for survival every three months. All patients must also be followed through completion of all protocol therapy. See Section 7.2.2 for additional details.

7 STUDY PARAMETERS

7.1 Therapeutic Parameters

- Screening procedures outlined on study calendar in Section 7.2. must be completed within 4 weeks prior to registration.
- Pre- study scans should be performed within 4 weeks prior to registration. Tumor assessment via CT or MRI will be optional at screening if data from standard care is available

- All patients must have a pre-dosing weight taken at every visit, as appropriate.
- All required pretreatment laboratory studies should be done as outlined in the study calendars in Section 7.2.
- Initial H&P and laboratory tests can be used for C1D1 if done within 72 hours

7.2 Observations and Tests

The schedule of events to be performed during the study is provided in **Table 7**. All assessments must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose of avelumab and/or intravesical BCG; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Table 7 Schedule of Events[l]

Cycles	**Screening**	**Induction Phase (cycle 1)[a]**				**Maintenance Phase**					**EOT**	**Follow-Up**
						(Month 3, 6, 12)				**Month 9**		
Weeks		**1-6**		**7-12**		**1-3**		**4-12**		**1-12**		
Days	**-28 to -1**	1	22	43	64	1		22	Q4W	Q4W		
Informed Consent	X											
Eligibility review	X	X										
History & Physical	X	X[b]	X	X	X	X		X	X	X		
ECOG-PS	X	X[b]	X	X	X	X		X	X	X	X	
Vital signs & weight	X	X	X	X	X	X		X	X	X	X	
Toxicity assessment [d]	X	X[d]									X	
Con-meds	X	X	X	X	X	X		X	X	X	X	
MRI / CT [c]	X	as clinically indicated										
CBC/Diff/ Plts [d]	X	X[b]	X	X	X	X		X	X	X	X	
Serum chemistry [e]	X	X[b]	X	X	X	X		X	X	X	X	
PT /PTT /INR	X	X[b]	If clinically indicated								X	

Cycles	Screening	Induction Phase (cycle 1)[a]				Maintenance Phase					EOT	Follow-Up
						(Month 3, 6, 12)				Month 9		
Weeks		**1-6**		**7-12**		**1-3**		**4-12**		**1-12**		
Days	**-28 to -1**	1	22	43	64	1		22	Q4W	Q4W		
Urinalysis [h]	X	X[b]	X	X	X	X		X	X	X	X	
TSH, FT3, and FT4	X	Repeat Q8W									X	
HIV, HBV, HCV serology	X											
Urine pregnancy test	X	X[b]	Repeat Q4W									
EKG [f]	X	If clinically indicated										
Blood sample for biomarkers [g]		X				X						
Urine sample for immunoassay [h]		X	X	X		X						
Avelumab IV dose [n]		X (Q1W)		X (Q2W)		X (Q1W)		X (Q2W)		X(Q2W)		
intravesical BCG		X (Q1W)				X (Q1W) C2, 3, 5					X	
Cystoscopy [m] and urine cytology [i]	X					Repeat Q3M as SOC						
QOL [j]		X				X					X	
Survival												X[k]

a. Treatment cycles are 84 days (12 weeks) long, with visits on Day 1 of each BCG course, then every 4 weeks coinciding with Avelumab infusion, unless otherwise specified. All visits have a window of ± 3 days (calculated in reference to Cycle 1/Day 1). The week following BCG therapy completion will not include avelumab treatment. Avelumab every two week therapy will start two weeks from the conclusion of BCG therapy and continue until the next BCG regimen. In the event

of an unforeseen event, such as a weather event, holiday, or center closure, the PI may alter treatment schedule by +/- 10 days to allow for resumption of therapy.

b. If history, PE, ECOG-PS and screening laboratory tests are performed within 72 hours prior to first dose (Cycle 1, Day 1), repeat testing is not required.
c. Tumor assessment via CT or MRI will be optional at screening if data from standard care is available.
d. **Toxicity assessment is required prior to each BCG and/or avelumab treatment**. If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will be also required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 3 weeks may resume.
e. Consisting of albumin, alkaline phosphatase, BUN, calcium, carbon dioxide (CO2), chloride, creatinine, glucose, potassium, AST, ALT, sodium, total bilirubin, total protein
f. Patients will undergo EKG monitoring at screening. Additional EKG at pre-dose on day 1 of each cycle and EOT if clinical indicated.
g. Blood sample for exploratory biomarkers will be collected at pre-dose on day 1 of induction therapy; and at pre-dose on day 1 of month 3 and month 6 maintenance therapy.
h. Urine sample will be collected at pre-dose on days 1, 22 and 43 of induction treatment; and at pre-dose on day 1 of Months 3 and 6 Maintenance for measurement by multiplexed immunoassay for immune response biomarkers.
i. Cystoscopy and urine cytology will be obtained at screening and at Month 3, 6, 9, and 12 and at EOT. Only frankly malignant cytology will be considered positive and used to determine the need for bladder biopsy and further evaluation.
j. Patient will be asked to complete EORTC QLQ-C30 to measure QOL on BCG [33].
k. Every three months for up to one year. See Sections 7.2.1 and 7.2.2 for additional details.
l. During the COVID-19 crisis, protocol mandated visits may be performed via telemedicine or visits may be combined in order to prevent imminent safety risks to patients. All such changes to the visit schedule must be clearly documented in the subject's chart. Changes in study visit schedules or missed visits must be explained in the final clinical study report.
m. For the subset of patients with CIS (with or without concomitant Ta or T1 disease) at study entry, a 6-month biopsy is required. A negative biopsy at 6 months will provide evidence of complete response. A +/- 10 day window will be allowed around the disease assessment time point. Patients receiving a second induction will not be required to undergo 6-month biopsy.
n. Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions.

7.2.1 Extended safety follow-up

Given the potential risk for delayed immune-related toxicities, safety follow-up may be performed up to 90 days after the last dose of avelumab administration.

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.

7.2.2 Tumor assessment during post treatment follow up

For patients who have completed 12 months of treatment without progressive disease or discontinued treatment for reasons other than PD, the tumor assessments by cystoscopy and urine cytology should be repeated every 3 months for one year as per standard of care or until tumor progression.

7.3 Biological Sample Collection for Translational Study

We will assess immune profile in the pre- and post- treatment urine and blood as potential biomarkers that would associate with tumor response from the combination of avelumab and intravesical BCG. The analysis of other molecular profile may be optional if sample of cystoscopy and urine cytology is available.

7.3.1 Urine collection:

Urine will be collected before BCG treatment on the following days:

BCG Induction phase:

- Week 1 day 1 (Day 1, before BCG treatment)
- Week 4 day 1 (day 22, before BCG treatment)
- Week 7 day 1 (day 43)

BCG maintenance phase:

- Day 1 of Month 3 and 6 Maintenance: before BCG treatment

Urine specimen will be sent to the Stephenson Cancer Center biorepository for storage, which will be analyzed using a multiplexed immunoassay if collaborative funding is available.

7.3.2 Blood collection:

Blood sample for exploratory biomarkers will be collected before BCG treatment on the following days:

BCG Induction phase:

- Week 1 day 1 (Day 1, before BCG and avelumab treatment)

BCG maintenance phase:

- Day 1 of Month 3 and 6 Maintenance: before BCG and avelumab treatment

Blood specimen will be sent to the Stephenson Cancer Center biorepository for storage, which will be analyzed for immune profile changes if collaborative funding is available.

7.3.3 Sample shipping

Blood and urine samples will be sent to the Stephenson Cancer Center biorepository for processing and biomarker testing (See lab manual for detailed instructions).

8 EVALUATION CRITERIA

8.1 Safety Evaluation

Toxicity assessment is required prior to each BCG and/or avelumab treatment. Toxicity and grades will be classified using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Dose limiting toxicity (DLT) will be monitored during the first 6 weeks of induction treatment with intravesical BCG and IV avelumab. Definition of DLT is described in section 5.2.1.

Completion rate of induction therapy with combined BCG + avelumab is defined as completion of at least 5 of 6 treatments of each BCG and avelumab within 8 weeks during BCG induction phase.

Six-month treatment completion rate will be based on patients' completion of at least 2 of 3 BCG treatments within each 5 week period at the 6 Month maintenance treatment.

8.1.1 Definition of Evaluable patients for Safety Analysis

Evaluable patients will be defined as patients who receive at least one dose of intravesical BCG and avelumab.

8.2 Efficacy Evaluation

Cystoscopy and urine cytology will be obtained at screening and at Month 3, 6, 9, and 12. Only frankly malignant cytology will be considered positive and used to determine the need for bladder biopsy and further evaluation. Three-month complete response (CR) rate, 6-month CR rate, recurrence free survival (RFS), cystectomy-free survival (C

FS), and overall survival will be evaluated as the following.

Time to High-Grade Recurrence (TTHGR) is defined as time from date of first treatment to first high-grade recurrence. Patients without a recurrence will be censored at their last cystoscopy date. Those who die without a recurrence are also counted as a recurrence and high-grade recurrence at time of death.

Time to Recurrence (TTR) is identical to TTHGR with the addition that failure with any-grade bladder cancer is considered an event.

Progression-free survival (PFS) is defined as time from date of first treatment to first evidence of muscle invasive bladder cancer, metastatic disease, or death due to any cause. Those without an event are censored at their last valid tumor assessment, or at the last tumor assessment before patient start of the new therapy if a patient has started new anti-cancer therapy.

Complete Response: For the subset of patients with CIS (with or without concomitant Ta or T1 disease) at study entry, a 6-month biopsy is required. A negative biopsy at 6 months will provide evidence of complete response. A +/- 10 day window will be allowed around the disease assessment time point. Patients receiving a second induction will not be required to undergo 6-month biopsy

Duration of Complete Response: For the subset of patients with CIS (with or without concomitant Ta or T1 disease) at study entry who achieve a CR, duration is defined as time from first documentation of CR to time of first high grade recurrence. Patients who remain CR at end of study (EOS) are censored at their last cystoscopy date.

Overall survival (OS) is defined as the duration from the first dose date of the study drug until death due to any cause. Patients who are still alive at EOS are censored on the date they will be last known to be alive. An exploratory analysis to determine OS at EOS will be estimated by the Kaplan-Meier method.

Patient Reported Outcomes:

The EORTC QLQ-C30: is a 30-item cancer-specific quality of life questionnaire developed to assess QOL endpoints [33]. The measure consists of 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), a global health status / quality of life scale, and additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia,

constipation and diarrhea) and perceived financial impact of the disease (https://www.eortc.be/qol/files/SCManualQLQ-C30.pdf). The EORTC QLQ-C30 is reliable and has discriminatory association with clinical status, disease stage, and symptom severity. Patients are asked to answer questions regarding their symptoms and/or quality of life on day 1 prior to BCG treatment during BCG induction phase and day 1 of BCG maintenance phase.

8.2.1 Definition of Evaluable Patients for Efficacy Analysis

Evaluable patients will be defined as patients who receive at least 5 doses each of intravesical BCG and avelumab IV during induction treatment (first 8 weeks) and complete the first post-treatment cystoscopy and/or urine cytology for tumor assessment. Patients who discontinued study treatment due to toxicity incurred by previous therapy will be evaluated for safety analysis, but will be replaced by additional patients for the efficacy analysis.

Patients removed from study for early withdraw or hypersensitivity reactions will be replaced if they have received less than 5 doses of study treatment during induction treatment, but will be included in the safety analysis.

Patients who do not receive at least 5 doses of intravesical BCG and avelumab IV during induction treatment will be considered unevaluable for efficacy analysis and will be replaced unless the missed doses were due to development of grade 3-4 adverse events related to study treatment.

9 SAFETY MONITORING AND REPORTING PROCEDURES

The safety plan for patients in this study is based on clinical experience with IV avelumab and intravesical-BCG in completed and ongoing studies. The anticipated important safety risks are outlined in sections 6.4.1 and 6.4.2.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of avelumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. After initiation of study treatment, all adverse events will be reported until 90 days for avelumab after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days for avelumab after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, is provided in section 6.4.

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern.

9.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 90 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment. Stopping rules for toxicity are defined in Tables 2-4 & 6.

The principal investigator is responsible for ensuring that all Aes and SAEs that are observed or reported during the study, are collected and reported to the FDA and appropriate IRB in accordance with CFR 312.32 (IND Safety Reports).

All reportable events should be sent to the Sponsor via email:

SCCIITreporting@ouhsc.edu

OR

Fax at 1-405-271-1416.

In addition, the principal investigator is responsible for notifying EMD Serono GPS in parallel of such events within 2 business days or 3 calendar days (whichever comes first) of the Sponsor/PI becoming aware of the event (ideally using the applicable safety report form provided by EMD). The following reportable events must be submitted to EMD Serono:

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

Fax: +49 6151 72 6914

OR

E-mail: ICSR_CT_GPS@merckgroup.com

Post-Study Adverse Events: The principal investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior avelumab and/or intravesical-BCG exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

9.1.1 Reporting Suspected Unexpected Serious Adverse Reactions

In compliance with FDA regulations, as contained in 21 CFR 312.32, all Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported by Stephenson Cancer Center, University of Oklahoma Health Sciences Center (the sponsor for this study) to the FDA within the required timeframes. Research staff should notify the PI within 24 hours of awareness of an SAE for timely evaluation of reportability to FDA.

The Sponsor/PI or designee is responsible for notifying EMD Serono Drug Safety within 2 business days or 3 calendar days (whichever comes first) of awareness.

Contact information for submission of reportable events to EMD Serono:

Fax: +49 6151 72 6914

OR

E-mail: ICSR_CT_GPS@merckgroup.com

Specifying:

PROTOCOL Number and/or Title

EMD Serono assigned Study Number

SUBJECT Number

SITE Number/PI Name

SAE/ONSET DATE

With the assistance of Stephenson Cancer Center Clinical Trial Office (SCC CTO), all SUSARs must be reported to the FDA by the investigator within 7 (serious criteria of death or life threatening) or 15 (all other seriousness criteria) calendar days of awareness.

Supporting and follow up data: Any supporting or follow up documentation must be submitted to the regulatory authorities per federal regulations and institutional standards when available. The Sponsor/PI or designee is also responsible for notifying EMD Serono Drug Safety about the supporting or follow up data.

9.1.2 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

1. Treatment regimen
2. Protocol description (and number, if assigned)
3. Description of event, severity, treatment, and outcome if known
4. Supportive laboratory results and diagnostics
5. Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

MedWatch 3500A (Mandatory Reporting) form is available at

http://www.fda.gov/medwatch/getforms.html

Follow-up Information:

Additional information may be added to a previously submitted report by any of the following methods:

1. Adding to the original MedWatch 3500A report and submitting it as follow-up
2. Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
3. Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally EMD Serono, may contact the sponsor/principal investigator for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact SCC CTO study's regulatory project manager at SCCIITreporting@ouhsc.edu.

9.2 Adverse Event Monitoring

9.2.1 Definitions (per 21 CFR 312.32(a))

Adverse event: "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

This includes the following:

1. Aes not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with study treatment that were not present prior to the AE reporting period.
2. Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as tumor biopsy).
3. If applicable, Aes that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
4. Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

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

Serious adverse event or serious suspected adverse reaction: "An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or A congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

Suspected adverse reaction: "Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."

Unexpected adverse event or unexpected suspected adverse reaction: "An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation."

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 CTCA version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of either avelumab, intravesical-BCG or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a non-serious AE
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTCAE Grade 5 (fatal outcome) indicated.

9.2.2 Definition of an Adverse Events of Special Interest

AESIs (serious or non-serious) are defined as Aes of scientific and medical concern specific to a product or program, for which ongoing monitoring and rapid communication can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor-Investigator to other parties (eg, regulators) might also be warranted.

Serious AESIs shall be forwarded to EMD Serono within 2 business days or 3 calendar days (whichever comes first) of the awareness date. Others shall be sent within thirty (30) calendar days.

9.2.2.1 Adverse Events of Special Interest for Avelumab

The adverse events of special interest for avelumab are summarized in tables 2-4 and detailed information can be found in avelumab Investigator's Brochure.

9.2.3 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

9.2.4 Pregnancy or Breastfeeding

If a patient becomes pregnant or breastfeeding while receiving avelumab or within 5 months after the last dose of avelumab, a report should be completed and expeditiously report to sponsor/principal investigator. Follow-up to obtain the outcome of the pregnancy should also occur.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported to sponsor/principal investigator, as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the avelumab should be reported to sponsor/principal investigator as an SAE.

Pregnancy reports: While such reports are not serious Aes or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Sponsor/Principal investigator within 2 business days or 3 calendar days of the awareness date (whichever comes first) using the applicable safety report form provided. Meantime, such reports shall be forwarded to EMD Serono within 2 business days or 3 calendar days (whichever comes first) of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

9.3 Documenting Adverse Events

All Aes information must be documented on the appropriate AE case report form. Additional follow-up information (e.g., test results, autopsy, and discharge summary) may be obtained to supplement AE reports. A copy of all initial and follow-up reports will be included with the patient's study files.

9.3.1 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting Aes or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis versus Signs and Symptoms: If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths: All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

Preexisting Medical Conditions: A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalizations for Medical or Surgical Procedures: Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

9.4 Causality Assessment of Adverse Events

The relationship between an AE and the study drug will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions.

An AE will be considered associated with the use of study drug if there is a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those Aes that are considered definitely, probably, and possibly related to the use of the study drug:

Definitely Related: An AE that follows a temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after stopping the study drug (positive dechallenge) and reappears after repeat exposure (positive rechallenge); and cannot be reasonably explained by known characteristics of the patient's clinical state or by other therapies

Probably Related: An AE that follows a reasonable temporal sequence from administration of the study drug; follows a known response pattern to the study drug; improves after dechallenge; and cannot be reasonably explained by the known characteristics of the patient's clinical state or by other therapies.

Possibly Related: An AE that follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug but could have been produced by the patient's clinical state or by other therapies An AE may be considered not associated with the use of study drug if there is not a reasonable possibility that the AE may have been caused by the study drug. This definition applies to those Aes that are considered unlikely or not related to the use of the study drug:

Unlikely to be Related: An AE assessed as unlikely to be related to study drug is defined as an AE for which sufficient information exists to indicate a high improbability that the event is related to the study drug.

Not Related: An AE assessed as not related to study drug is defined as an AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug. Two or more of the following variables apply:

- The AE does not follow a reasonable temporal sequence after administration of the study drug.
- The AE is readily explained by the patient's clinical state or other therapies.
- Negative dechallenge—the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval).

9.5 Severity Assessment of Adverse Events

Severity of Aes will be graded according to the CTCAE Version 5.0.

Adverse events not included in the CTCAE, Version 5.0 must be graded as follows: Mild, Moderate, Severe, Life-threatening, and Fatal according to the following definitions:

- Mild: The AE is noticeable to the patient but does not interfere with routine activity.
- Moderate: The AE interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- Life-threatening: The AE places the patient at risk of death at the time of the event.
- Fatal: The AE results in the death of the patient.

9.6 Study Monitoring

All aspects of the study will be carefully monitored at periodic intervals throughout the study per FDA "Guidance for Industry – E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1)" dated March 2018. All Case Report Forms (CRFs) will be up to 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each patient. The monitoring visits provide the PI with the opportunity to evaluate the progress of the study, to verify appropriate consent form procedures, review drug accountability and to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records and to assure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

Furthermore, this study will fall under the purview of the Stephenson Cancer Center Data Safety Monitoring Committee (DSMC).

9.7 Data Disclosure and Patient Confidentiality

Patient medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency inspectors, the clinical trial office auditors and monitors, University of Oklahoma Office of Compliance, and the Investigational Review Board (IRB).

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number and/or initials to maintain patient confidentiality. All study records will be kept in a locked file cabinet or other secured area. All computer entry and networking programs will be identifiable only by coded numbers and/or initials. Patient personal medical information may be reviewed by representatives of the Sponsor, of the IRB of record, University of Oklahoma Office of Compliance, or of regulatory authorities in the course of monitoring the progress of the clinical trial. Every reasonable effort will be made to maintain such information as confidential.

10 STATISTICAL CONSIDERATION

10.1 Consideration for Sample Size

The primary objective is to ensure patients can tolerate a complete induction course of combination therapy as defined by the ability to receive at least 5 of 6 treatments of BCG + avelumab within eight weeks of starting treatment. By using a modified 3+3 design for DLT observation, we expect to enroll 3~6 patients for dose level 1. If dose level 1 is not tolerated, then an additional 3~6 patients will be enrolled in dose level -1.

The most important secondary objective is to evaluate the feasibility of remaining on combination treatment to complete Month 6 maintenance therapy without dose-limiting toxicity. Therefore, an additional 12~15 patients will be enrolled and will receive the final dose. The proportion of patients completing Month 6 maintenance will be calculated and a 95% confidence interval constructed for the completion rate. The expected completion rate is about 60%. However, the final sample size was obtained from feasibility and not formal power analysis. With 18 patients at the final dose and an expected completion rate of 60%, the lower bound of the two-sided Wilson Score 95% confidence interval (CI) would be 37.6%. Although this lower limit was not clinical meaningful, it is provided to show the width of the CI given a desired 60% completion rate and the small sample size.

In order to enroll 18 evaluable patients for dose expansion cohort, we may need to screen up to 27 patients if dose level -1 will be evaluated as the final dose level since we expect a percentage of these patients to be screen failures or withdrawals.

10.2 Analytic Plan

Only evaluable patients as defined in Section 8.1.1 will be included in the statistical analysis. The proportion of patients receiving a complete induction course (at least 5 of 6 treatments of each BCG and avelumab within eight weeks of starting treatment) at 3 months and at 6 months will be calculated and a 95% Wilson score confidence interval constructed for the completion rate.

The 3-month and/or 6-month complete response (CR) rates will be summarized as the proportion (and 95% CI) of patients with complete tumor response at month 3 or 6 of study treatment.

Kaplan-Meier curves will be generated for overall survival, duration of response, progression-free survival, cystectomy-free survival, time to recurrence, and time to high-grade recurrence. Median survival time and 95% confidence intervals will be calculated. The EORTC QLQ-C30 questionnaire functional scales, symptom scales, and global health and quality of life scale will be summarized.

Frequency and severity of adverse events will be tabulated by body system, type and maximum grade. Serious adverse events will be listed.

Interim analysis

An interim safety analysis will be conducted when 3~6 patients have received ≥ 5 doses of BCG treatment in dose level 1. If the combination therapy in dose level 1 is not tolerated (2 or more patients experience a DLT), dose level -1 will be evaluated in additional 3~6 eligible patients. The decision rule is fully described in Section 5.2 Overall Study Design.

10.3 Accrual and Study Duration

This is a single arm, phase Ib study. Total 18 evaluable patients will be enrolled in the Stephenson Cancer Center. More than 40 patients with bladder cancer will initiate intravesical BCG treatment in our Urologic Oncology clinic each year, including approximately 40% patients with BCG-treated but unresponsive NMIBC (persistent or recurrent) who are hopefully eligible for the proposed study. Based on our prior experience with similar patient population, we anticipate enrollment of 1 patient per month.

The planned sample size is 18 evaluable patients for dose expansion cohort. Conservatively allowing for up to 10% dropout, we will enroll up to 27 patients for an evaluable 18. Thus the maximal study period will be 54 months (30 months accrual plus 12 months study treatment plus 12 months survival follow-up). It is assumed that is sufficient to observe the minimum number completed cycles and to assess the time-to-event variables, including recurrence free survival and OS.

11 DATA AND SAFETY MONITORING PLAN

Safety oversight will be performed by Stephenson Cancer Center's (SCC) internal Data and Safety Monitoring Committee (DSMC). The DSMC is composed of individuals with the appropriate expertise in adult and pediatric hematology and medical oncology, radiation oncology, translational and correlative science, pharmacy, nursing and biostatistics. The DSMC operates under the rules of an approved data safety monitoring plan which complies with the National Cancer Institute (NCI) guidelines published as *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by NCI* as of January 2005 and the "*NIH Policy for Data and Safety Monitoring*," *NIH Guide for Grants and Contracts*, http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The Data Safety Monitoring Committee is charged with oversight of participant safety, study conduct and the validity and integrity of data for clinical trials at SCC. While the focus of the DSMC is to monitor interventional investigator initiated trials (IITs) that are not subject to external monitoring, it has the authority to monitor any SCC protocol when potential concerns are identified. The DSMC also has the authority to suspend or close a study until the principal investigator addresses any issues that may cause harm or increase risks to subjects. The DSMC reports all findings to the Institutional Review Board (IRB).

Under the direction of the DSMC chair, a full board meeting is convened on a quarterly basis to review the accumulated safety data, accrual information, and additional information as stated in the DSMC plan.

11.1 DSMC Auditing

In addition to monitoring, the DSMC oversees an internal auditing process to ensure subject safety and data quality. All cancer-related clinical trials active at the SCC are eligible for audit; however, priority is placed on those clinical trials that are not monitored or audited by an outside entity. If an external entity conducts an audit of a clinical trial at the SCC, then the findings of that audit are reported to the DSMC,

either through the formal audit report provided by the external auditing entity, if available, or from the PI, who will report any findings communicated during the audit process.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Quality Assurance

Stephenson Cancer Center (SCC) will be responsible for clinical monitoring of all data for this study.

12.2 Electronic Database and Case Report Forms

The Principal Investigator and designated team will develop a study-specific electronic database in REDCap and study-specific case report forms (CRF) for study data entry. All study data will be recorded into the REDCap database sponsored by OU-SCC and stored in a 21 CFR 11 compliant database. Only the Principal Investigator and assigned research staff will have access to the study data. The electronic case report forms will be available to EMD Serono, the IRB of record, and regulatory authorities in event of an audit or inspection.

12.3 Record Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

The Investigator will retain all research documents and case report forms at study site per federal requirements and institutional policy.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Ethical Conduct of the Study

The study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki in addition to the requirements of the ICH E2A guidelines. This study will also comply with U.S. FDA regulations under a U.S. Investigational New Drug (IND) application in addition to local, state, and federal laws.

13.2 Informed Consent

The informed consent document will be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent document used in this study and any changes made during the course of the study will be prospectively approved by the IRB of record.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The study site will retain the original of each patient’s signed consent document. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

13.3 Institutional Review Board or Ethics Committee

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs per IRB policy.

The Principal Investigator is required to promptly notify the IRB of all adverse drug reactions that are both serious and unexpected per IRB policy. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by EMD Serono, Inc (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.) per IRB policy.

13.4 Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

13.5 Protocol violations/deviations

The investigator will conduct the study in compliance with the protocol. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

When immediate deviation from the protocol is required to eliminate an immediate hazard to patients, the Investigator will contact the Sponsor or its designee if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation.

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