Mayo Clinic Cancer Center

Phase II study evaluating combination chemotherapy + Radiotherapy (RT) with avelumab in muscle invasive bladder cancer.

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Drug Availability:

Commercial Agents: 5 – Flourouracil, mitomycin, cisplatin
Drug Company Supplied: avelumab

√Study contributor(s) not responsible for patient care

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted], Data Manager Phone: [redacted]
Forms completion and submission	[redacted] (Arizona Coordinator) Phone: [redacted] [redacted] (Arizona Data Coordinator) Phone: [redacted]
Protocol document, consent form, regulatory issues	[redacted] Sr. Research Protocol Specialist
Serious Adverse Event Reporting	[redacted] SAE Coordinator

*No waivers of eligibility allowed

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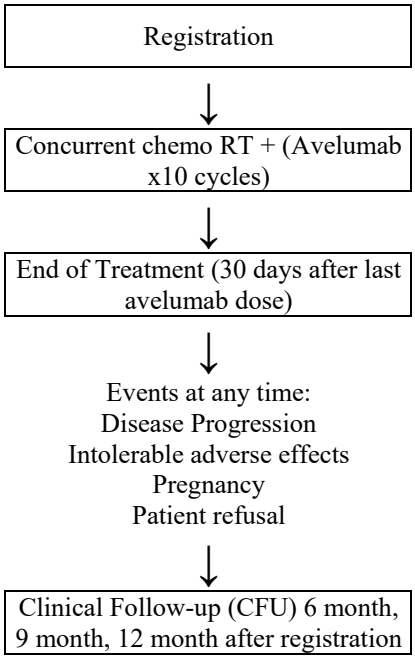
Schema

For the run-in portion only, prior to discussing protocol entry with the patient, call the MCCC Registration Office ([redacted]) to insure that a place on the protocol is open to the patient.



Cycle = 14 days

NOTE: All cycles will be based on avelumab given once every 14 days.
Chemo therapy may be given as clinically indicated and any delays are per healthcare provider's discretion. Radiation therapy to be given as clinically indicated per section 7.2. Options for concurrent chemotherapy (Providers choice) listed below. They do not affect the cycle length. (See Section 7.1)

Generic name: avelumab Brand name(s): Bavencio Mayo Abbreviation: *AVELUMAB* Availability: Drug company providing to Mayo Clinic Pharmacy	Generic name: 5-fluorouracil Brand name(s): Adrucil Mayo Abbreviation: *5FU* Availability: Commercial
Generic name: mitomycin Brand name(s): Mutamycin Mayo Abbreviation: *MITOC* Availability: Commercial	Generic name: cisplatin Brand name(s): Platinol Mayo Abbreviation: *CDDP* Availability: Commercial

1.0 Background

1.1 Defining clinical unmet need

In the US alone over 75,000 new patients are diagnosed every year with bladder cancer and the median age is 73 years. Treatment patterns in the community consistently demonstrate that despite potential lethal outcomes, many patients with bladder cancer do not receive appropriate aggressive and potentially curative therapy. Analysis of over 28,000 patients with T2-T4a bladder cancer in National cancer database showed that only 52% patients received aggressive therapy for their bladder cancer and over 25% patients received observation only. [1] As our population is aging, the predominant proportion of the newly diagnosed patients are elderly and they are even at higher risk of not receiving appropriate care. A recent NCDB analysis evaluated over 9000 patients diagnosed with bladder cancer with age greater than 80. [2] They observed that only 4.2 percent of the patients received standard of care chemotherapy followed by radical cystectomy, while 44% underwent TURBT alone. A study looking at data from the SEER database demonstrated that only 21% of patients received radical cystectomy for stage II or higher bladder cancer. At the same time radical cystectomy can potentially be a life changing event for many patients. Even in experienced specialized centers, radical cystectomy entails a high risk of morbidity(up to 60%) and mortality of up to (2.5%)[3] A number of patients may not be fit for or refuse radical cystectomy . These data clearly indicate the need to improve access to definitive therapy and to test strategies to improve the outcomes with CRT.

Combined analysis of RTOG/NRG patients enrolled on concurrent CRT trials has shown a complete response rate of 69% with five-year overall survival of 57% and disease-specific survival of 71%.[4, 5] In a propensity-matched retrospective analysis the group from Princess Margaret Hospital in Toronto reported no differences in 5-year disease-specific survival between trimodality therapy and radical cystectomy (RC) (76.6% vs. 73.2%, p=0.49).[6] In a recent 2017 guideline paper from collaborative panel of experts from American Urological Association, American Society of Clinical Oncology, American Society of Radiation Oncology and Society of Urologic Oncology recommended that bladder preservation therapy is the preferred treatment for patients desiring bladder preservation and understand the unique risks associated with this approach and/or those who are medically unfit for surgery.[19]

1.2 Development of concurrent CRT in bladder cancer

Cisplatin as single agent or in combination with 5-FU had traditionally been the drug of choice for radio- sensitization. Earlier trials investigated the role of neoadjuvant chemotherapy prior to radiation alone and demonstrated 6% absolute survival advantage at 10 years.[8]. Subsequent trials investigated the role of neoadjuvant chemotherapy followed by CRT. In one of these trials, RTOG 89-03, patients were randomized to concurrent CRT with or without neoadjuvant chemotherapy. The trial was prematurely closed when an increased incidence of neutropenic complications was observed. The analysis of enrolled patients showed no significant benefit of neoadjuvant chemotherapy.[9] In the large phase III trial BC2001, where neoadjuvant chemotherapy was allowed but not mandated, one third of patients received neoadjuvant chemotherapy. The primary endpoint of loco-regional disease control was not different in the group receiving neoadjuvant chemotherapy as compared to the one without chemotherapy. BC2001 also demonstrated that an alternative chemotherapy regimen, 5- fluorouracil and mitomycin, can be used effectively, including in patients with poor renal function who

are cisplatin-ineligible. The overall loco-regional disease free survival at 2 years were 67% in the CRT group and 54% in the radiotherapy group(HR=0.68 , p=0.03)This trial also investigated two different radiotherapy schedules and doses in a 2-by-2 randomizations, 55 Gy in 20 fractions vs 64 in 32 fractions and whole –bladder vs modified volume radiotherapy. There was no observed difference in outcomes between the schedules.[10] The recent updated results of BC2001 continue to show no difference in OS or metastases free survival between the groups receiving or not receiving neoadjuvant chemotherapy.[11] A small phase II trial evaluated weekly gemcitabine and 52.5 Gy radiation in 20 fractions. Complete response was observed in 88% of patients at the time of first post treatment cystoscopy. One patient underwent cystectomy for toxicity and 1 patient had bowel toxicity requiring bowel resection. Overall durable local control and acceptable toxicity were observed in the treated patients.[12] This led to a larger phase II trial by RTOG/NRG (0712) evaluating gemcitabine versus 5 –FU and cisplatin combined with radiotherapy. The data was presented at ASTRO 2017 showing safety and efficacy of gemcitabine in combination with radiation in bladder cancer. A number of Canadian groups (Princess Margaret Hospital - personal communication) are already using gemcitabine as standard chemotherapy with radiation.

Despite improvements in chemotherapy options and radiation therapy technology, the outcomes with patients with bladder cancer remain poor with less than 50% surviving 5 years. Bladder preservation strategies need to evolve in order to improve long-term outcomes for the growing need of patients who are ineligible for full dose cisplatin based neoadjuvant chemotherapy and/or are either refusing or ineligible for radical cystectomy.

Table 1 summarize the results from various bladder preservation trials

Study	*Dose*	*Chemotherapy (doses in mg/m2)*	*N*	*CR*	*5-yr Intact Bladder*	*5-yr LRFS*	*5-yr OS*
85-12[13]	**64 Gy**	**C100**	**47**	**66 %**	**42%**	**45%**	**52%**
88-02[14]	**39.6 Gy**	**NAC M30 + C70 + V3 → C70**	**90**	**75 %**	**44% (4yr)**	**45% (4yr)**	**51%**
89-03[9]	**64.8 Gy**	**NAC M30 + C70 + V3 → C100**	**123**	**59 %**	**38%**	**60%**	**49%**
95-06[15]	**44 Gy (BID fxns)**	**C15 + 5FU400 (3d x wkly)**	**34**	**67 %**	**66% (3yr)**	**65% (3yr)**	**83% (3yr)**
97-06[16]	**64.8 Gy (BID fxns)**	**C20 (2d x wkly)**	**47**	**74 %**	**48% (3yr)**	**73% (3yr)**	**61% (3yr)**
99-06[17]	**64.3 Gy (BID fxns)**	**C20 + P50 (2d x wkly) → GC x 4 (Adj)**	**81**	**87 %**	**69% (2yr)**	**NR**	**79% (2yr)**
02-33[18]	**64.3 Gy (BID fxns)**	**C15 + 5FU400 / C15 + P50 (3d x wkly) → GCP (Adj)**	**93**	**NR**	**NR**	**NR**	**73% (2yr)**
TROG 9701/9906[19]	**64 Gy**	**C35 (1d x wkly)**	**116**	**70 %**	**61%**	**45%**	**50% (DSS)**

BC2001 [10]	**55-64 Gy**	**5FU500 + MMC12 (5d CI)**	**360**	**NR**	**89% (2yr)**	**82% (2yr)**	**48%**

Table 1: CRT Clinical Trial Results [9, 10, 13-19]

(N = number of patients, CR = complete response rate, yr = year, LRFS = local relapse free survival, OS = overall survival, Gy = gray, C = cisplatin, NAC = neoadjuvant chemotherapy, M = methotrexate, V = vinblastine, BID = twice daily, fxns = fractions, 5FU = 5-fluorouracil, d = days, wkly = weekly, P = paclitaxel, G = gemcitabine, Adj = adjuvant chemotherapy, NR = not reported, TROG = Tazmanian radiation oncology group, DSS = disease specific survival, MMC = mitomycin C, CI = continuous infusion)

1.3 Rationale for combining immune checkpoint inhibition and concurrent chemo radiation

In recent years checkpoint inhibitor therapy (CPI) has been approved for multiple cancer types including bladder cancer. These drugs have shown significant activity in patients who are cisplatin ineligible and those that have progressed following treatment with first line platinum based chemotherapy[11, 20-23]. These drugs are known for their durability of response and excellent tolerability but limited overall response rate.

Both chemotherapy and radiotherapy have pleiotropic effects on the immune system that can potentially trigger an antitumor response. It has been shown in pre-clinical and clinical settings that checkpoint inhibition in combination with either modality of therapy can augment and sustain this antitumor activity. For example, Apetoh et al. demonstrated the emission of a danger signal known as high mobility box binding protein-1 (HMGB1) from dying tumor cells in response to either chemotherapy or radiotherapy.[24] Tumor HMGB1 expression in combination with toll-like receptor-4 (TLR4) expression on dendritic cells was shown to be prerequisites for effective tumor antigen presentation. Another example is demonstrated with anthracyclines, which are used in the treatment of both NMIBC and MIBC. Anthracyclines induce rapid production of type I interferons, which in turn induce chemokine ligand 10 (CXCL10) release which is intricately involved in tumor cell death. [25] Wu et al. demonstrated in cell lines that radiation can induce PD-L1 expression in tumor cells and addition of a PD-L1 inhibitor to radiation decreased cell proliferation and augmented cell death. [26] The same group investigated PD-L1 expression in pre-treatment biopsies in patients who had received concurrent CRT for bladder cancer. They observed that high PD-L1 expression was significantly associated with lower complete response rates after CRT. Recently published studies in non-small cell lung cancer demonstrated superior efficacy and safety of combining checkpoint inhibitors and chemotherapy vs. chemotherapy alone leading to a change in treatment paradigm[27] In a retrospective series of lung cancer patients who had received prior radiation, either- concurrent with or following checkpoint inhibition therapy, the authors observed a modest increased risk of severe side effects especially in the group receiving radiation after immunotherapy.[28] Multiple groups have published their experience in melanoma and lung cancer with combining radiation and checkpoint inhibitors reporting abscopal effects raising the possibility of not only improving local control but also of reducing systemic recurrences.[29, 30].

Data from these studies is hypothesis generating and suggest that a combinatorial strategy of CRT and checkpoint inhibition could improve outcome in localized muscle invasive bladder cancer. There is potential for an increase in local GI, GU and systemic immune-related side effects that would need to be balanced with the potential benefit of

combination therapy. There is clearly an unmet need to optimize the integration of these therapies in order to lower the impact of potential antagonistic interactions and also assess additive toxicity.

In this study we are testing the efficacy of avelumab in combination with concurrent CRT. Avelumab, (MSB0010718C) is an investigational fully human anti–PD-L1 IgG1 antibody that inhibits PD-1/PD-L1 interactions while leaving the PD-1/PD-L2 pathway intact. This enhances immune activation against tumor cells. Unlike other anti–PD-L1/PD-1 antibodies that are approved or in advanced clinical development, avelumab induces lysis of tumor cells via antibody-dependent cell-mediated cytotoxicity in vitro, suggesting an additional mechanism of action. Importantly, avelumab has not shown antibody-dependent cell-mediated cytotoxicity against immune cell subsets in humans. In a large phase Ib study evaluating range of tumor types, avelumab showed activity in a 44 patient cohort of patients with metastatic urothelial carcinoma refractory to chemotherapy. Subsequent study including two hundred and forty two patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum containing chemotherapy. The confirmed overall response rate was 13 % at 13 week follow up. Toxicities were consistent with this class of drugs with 5.5% of patients having grade 3-4 treatment related toxicity. Based on this study it received approval for use in patients with urothelial carcinoma who have progressed on platinum containing chemotherapy. The proposed study will be a phase II single arm trial evaluating combination of chemoradiation with avelumab in patients with T2-T4a N0M0 bladder cancer. The trial has built in safety run in of 6 patients and accrual will be stopped to evaluate toxicity after 6 patients are enrolled.

1.4 Safety data from combination of immunotherapy and radiation or chemotherapy.

Safety of immunecheckpoint inhibitors in combination with chemoradiation for bladder is not established. However there is data from other tumor types which shed light on activity and potential adverse events. Pembrolizumab was recently approved in combination with chemotherapy in lung cancer. This approval was based on a phase III trial as mentioned above. The most common immune-mediated adverse events of any grade in avelumab plus chemotherapy groups were hypothyroidism(15%), hyperthyroidism(8%) and pneumonitis (5%).Overall no significant increase in toxicity as compared to chemotherapy alone arm. Interestingly, in a previous trial evaluating avelumab alone vs physician choice chemotherapy in lung cancer, hypothyroidism was observed in (9%) of patients, hyperthyroidism (7.8%) and pneumonitis (5.8%). Another phase III study evaluating durvalumab consolidation after definitive chemoradiotherapy in lung cancer observed 3.4% grade 3-4 immune related side effects vs 2.6% in the placebo arm. [31] This lead to recent apporval of durvalumab in lung cancer for maintainence therapy after concurrent chemoradiation.

There is ongoing phase I/II trial of gemcitabine with radiation and pembrolizumab for muscle invasive bladder cancer at New York University hospital. Among 6 patients enrolled by December 2017 one patient had dose limiting toxicity of diarrhea which responded to steroids.(personal communication with Arjun Balar, MD) another similar trial opened through Australian and New Zealand Urogenital and Prostate cancer trials group is evaluating pembrolizumab with cisplatin and radiation for localized muscle invasive bladder cancer. The trial has enrolled 4 patients who all have finished their concurrent chemoradiation and are currently on adjuvant avelumab by December 2017(personal communication Andrew Weickhardt, MD) . None of the patients had any grade 3-4 toxicity which would require treatment delays.

No published safety data exist with avelumab or any other checkpoint inhibitor therapies in patients receiving definitive pelvic radiation doses of up to 64.8 Gy as is standard in MIBC. IMpower132 is evaluating atezolizumab in combination with cisplatin and pemetrexed in lung cancer and safety analysis is expected in first quarter of 2018.

Atezolizumab is also being investigated in a phase II trial in combination with concurrent chemotherapy and radiation in lung cancer at MD Anderson cancer center. In personal communication with the Stephen Li(PI) 25 patients have been enrolled on to the study. Fifteen patients have finished their protocol assigned treatment with only one patient having immune related pneumonitis. This patient was taken off atezolizumab and responded to steroids and recovered completely. No excess toxicity was observed and all patients completed the protocol assigned concurrent chemoradiation therapy.

While the safety data of avelumab is impressive thus far, MIBC patients represent a patient population in which the goal of therapy in not only cure of bladder cancer but also reduce morbidity associated with the treatment. This proposal will give us insights into the safety of combining immune check point inhibitor with concurrent chemoradiation. Therefore this trial has been designed to evaluate both early signals of safety and maintain close monitoring throughout the trial for any excessive toxicity. The translational work associated with the clinical trial will help prepare for preliminary data for similar proposal that we will prepare for the phase III clinical trial which PI is preparing for NCI.

1.5 Correlative Research

It is becoming increasingly recognized that cancers can thrive upon evading the immune system. Malignancies such as urothelial carcinoma, melanoma and renal cell carcinoma are known to exploit the programmed death 1 (PD-1) pathway in order to evade the immune system through adaptive immune resistance. [1-3] Monoclonal antibodies targeting PD-1 have recently been introduced, and have been shown to improve survival when used in patients with advanced bladder cancer who have previously failed prior cisplatin based chemotherapy or are ineligible for chemotherapy.[1, 4-6]

The success of PD-1 blockade therapy in treatment of solid cancers is dependent on the presence of pre-existing tumor-reactive CD8+ T lymphocytes[3, 7]. Sharma et al had shown previously that patients with advanced urothelial carcinoma have higher numbers of CD8+ TILs within the tumor. They also observed positive correlation of advanced stage and better disease free survival and overall survival with higher number of CD+8 cells. [7]We and others have established that PD-1 and CD11a can be used to identify tumor-reactive CD8+ cytotoxic T lymphocytes in the peripheral blood or in tumor tissues [8-10]. We observed that patients with advanced cancers have high levels of CD11ahighPD-1+ CD8+ T cells in peripheral blood [8].

Bim (BCL-2-interacting mediator of cell death) is a downstream pro-apoptotic signaling molecule of PD-1 in antigen-primed CD8+ T-cells [11]. Interaction of PD-L1 (the ligand expressed on tumor cells) with PD-1 (on the cell surface of T-cells), leads to the upregulation of Bim in tumor-reactive (PD-1+ CD11a high) CD8+ T-cells [2]. Given that Bim is a pro-apoptotic mediator, this upregulation essentially leads to the removal of tumor-reactive effector CD8+ T-cells from the memory pool, which leads to tumor resistance to the immune system.[2] Interestingly, in patients with metastatic melanoma who did not receive anti-PD-1 therapy, high levels of Bim in circulating PD-1+ CD11a high CD8+ T-cells predicted poor survival, while it was predictive of clinical benefit with treatment using anti-PD-1 therapy. Furthermore, the frequency of Bim+ PD-1+ CD11a+ CD8+ T-cells decreased in responders to anti-PD-1 therapy, but not in non-responders.

[2] All this data and common theme in response to immune therapy among various solid tumors begs investigation in bladder cancer which is a solid tumor in which immunotherapy appears to be very effective in select group of patients. It remains to be evaluated whether high levels of Bim in circulating PD-1+ CD11a high CD8+ T-cells are associated with more aggressive disease in bladder cancer and it's eventual impact on outcomes with concurrent chemoradiation and immunotherapy.

On the other hand, we recently identified that CX3CR1 defined a PD-1 therapy-responsive CD8+ T cells with effector memory phenotype and function. In responders to PD-1 therapy or combined (chemotherapy), CX3CR1 identified an increased CD8 T cell population with effector function and endure cytotoxic chemotherapy drugs. Thus, measurement of CX3CR1+ among CD11a high CD8 T cells will give us a full coverage of therapy-responsive T cell population for understanding the potential cellular mechanism underlying clinical outcomes in patients following immunotherapy or combined therapy.

Myeloid-derived suppressor cells (MDSCs) which comprise of heterogenous population of cells consisting of myeloid progenitor cells and immature myeloid cells have been associated with cancer progression and tumor – induced immune dysfunction in variety of solid and hematologic malignancies including bladder cancer. MDSCs cells observed in bladder cancer expressed CD11b+CD33lowHLA-DR−CD3− . CD11b+CD33lowHLA-DR−CD3− cells were significantly higher peripheral blood in bladder cancer patients as compared to healthy donors and correlated with advanced stage (Ta/T1 vs T2-4). In a Mayo study of prostate cancer patients undergoing salvage lymphadenectomy, we evaluated compared CD14+ monocytic and CD14- granulocytic MDSCs, and found that the latter exhibited immunosuppressive activity with high expression of PD-L1 (Sharma, Dong and Karnes; unpublished). Given the presence of a systemic immune dysfunction in BC, this warrants further study in patients with BC. Specifically, it is unclear whether higher MDSC levels (and the relative proportions of the granulocytic and monocytic subtypes) in the peripheral blood are associated with adverse clinical outcomes after concurrent chemoradiation and immunotherapy.

Clinical response to chemoradiotherapy (CRT) combined with immunotherapy (CIRT) may be predicted by both genomic and immune-based markers (1, 2). It is anticipated that the addition of immunotherapy to CRT will improve the immune response to bladder-directed CRT by global alteration of T-cell function. Augmented response to combination CRT and immunotherapy (CIRT) may occur by several mechanisms including 1) increased numbers of neoantigens, 2) induction of tumor antigen-specific immune response after CRT resulting in cross presentation of released tumor antigens by dendritic cells in draining lymph nodes and 3) reversal of T-cell exhaustion by immune checkpoint inhibitors leading to improved clinical response compared to CRT alone (3).

A large single arm phase II trial (IMvigor210) with two large independent parallel bladder cancer cohorts (310 and 119 patients) showed that higher TMB was very strongly associated with higher response rate and longer overall survival with atezolizumab ($P < 0.0001$; Rosenberg et al. Lancet 2016; Balar et al. Lancet 2016). In the confirmatory large IMvigor 211 phase III clinical trial, 931 bladder cancer patients were randomized to atezolizumab or chemotherapy. In patients with higher TMB (N=274), overall survival was longer with atezolizumab vs. chemotherapy (median 11.3 months [95%CI 8.7–13.2] vs 8.3 months [7.2–10.4]; HR 0.68, 95%CI 0.51–0.90), while in patients with low TMB (N=270), survival was similar in treatment arms (median 8.3 months [6.4–9.8] vs 8.1 months [6.2–10.4]; 1.00, 0.75–1.32 (Powles T et al. Lancet 2017). Moreover, higher TMB correlated with better response to immunotherapy in a variety of tumor types

(Goodman AM et al. Mol Cancer Ther. 2017;16(11):2598-2608). In addition, recent data support that the large proportion of mutant neoantigens in mismatch repair-deficient tumors, as well as those with DNA damage response gene mutations, render them sensitive to immune checkpoint blockade in several solid tumors, including bladder cancer (Le DT et al. Science. 2017;357(6349):409-13; Teo et al. 2017 ASCO Meeting; Iyer et al. 2017 ASCO Meeting). Therefore, a critical goal is to assess predictors of response to local and systemic immune activity.

The predicted somatic neoantigenic load is a product of the somatic TMB. Somatic mutations result in the formation of altered peptides recognized as ‘‘non-self’’ by the immune system . These 9- to 11-amino acid peptides termed nonamers are subsequently presented in the major histocompatibility complex (MHC)- class I context and recognized by cytotoxic T cells . This suggests that a high mutational burden would evoke a more robust antitumor immune response that could be reinvigorated by ICIs. Several studies show the correlation between mutational load and response to ICIs in advanced UC13 and other cancers . In primary muscle-invasive bladder UC, patients with fewer neoantigens have shorter RFS compared to those with a high neoantigenic load..

The predicted neoantigenic burden was previously reported as a favorable prognostic indicator of increased patient survival in six major cancer types (colorectal, ovary, breast, brain, kidney, and lung). Inferring the MHC haplotypes from the sequence of germline DNA and combining this information with somatic mutational data can help predict mutant nonamers that can bind to patients’ specific MHC complexes.

PD-L1 expression was previously thought of a possible predictor of response to IO therapy. Multiple studies published in bladder cancer failed to make that correlation. Keynote 045 , Phase III randomized trial evaluating pembrolizumab vs chemotherapy in secondline setting in patients who had previous platin based therapy had co primary end points among all patients and among patients who had a tumor PD-L1 ligand combined positive score of 10% or more. The results showed no significant difference in duration of OS and PFS among total population and the group who had PD-L1 CPS of 10% or more. (p=0.24) Similar study ImVigor 211 evaluating atezolimab vs chemotherapy in second line setting in patients with advanced urothelial carcinoma showed no difference in outcomes in overall survival among two treatment arms clearly indicating that may be PD-L1 is not a good predictive but a prognostic marker. In our study we will evaluate PD-L1 expression on the immune and tumor cells using panel of antibodies available at Mayo and assess its correlation to response with chemoradiation.

Hypothesis:

1. Concurrent chemo-immuno- radiotherapy is safe and efficacious for patients with bladder cancer opting for bladder salvage.

2.0 Goals

2.1 Primary Goal

2.11 To evaluate the complete response rate of concurrent chemotherapy radiation treatment combined with avelumab for patients with muscle invasive bladder cancer.

2.2 Secondary Goals

2.21 To evaluate the safety and toxicity (adverse event profile) of concurrent chemotherapy radiation treatment combined with avelumab.

2.22 To evaluate quality of life (QoL) at 1 year of concurrent chemotherapy radiation treatment combined with avelumab.

2.23 To evaluate progression-free survival and relapse-free survival at 1 year with concurrent chemotherapy radiation treatment combined with avelumab.

2.3 Correlative Research

2.31 To explore biomarkers that may predict response to avelumab in the muscle invasive population. The following markers will be tested:

- Expression of PD-L1 and CD8 by immunohistochemistry (IHC)
- Expression of immune signatures by RNA-sequencing (RNA-seq).
- To evaluate the association of tumor mutational burden with response to concurrent chemo- radiation and immunotherapy
- To evaluate whether concurrent chemoradiation and immunotherapy after maximal TURBT is associated with a decrease in circulating $Bim^{+}CD11a^{high}PD\text{-}1^{+}CD8^{+}$ T-cells and MDSCs.

3.0 Registration Patient Eligibility

For the run-in portion only, prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] to insure that a place on the protocol is open to the patient.

3.1 Registration – Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histologic proof of T2-T4a N0M0 (AJCC 8th edition) with predominant urothelial carcinoma. Mixed histologies are acceptable provided urothelial carcinoma is the predominant histology. Small cell urothelial carcinoma is excluded.

3.13 Cystoscopy with maximal TURBT performed ≤ 70 days of study registration. NOTE: Both completely resectable or partially resectable tumors are eligible as long as the treating urologist attempted complete resection. Exam under anesthesia needs to be performed and documented.

3.14 The following laboratory values obtained ≤ 28 days prior to registration.

- ANC ≥ 1500/mm^3
- PLT ≥ 100,000/mm^3
- Total bilirubin ≤ 1.5 upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤ 2.5 x ULN (≤5 x ULN for patients with liver involvement)
- Alanine Aminotransferase (ALT) ≤ 2.5 x ULN (≤5 x ULN for patients with liver involvement)
- Hgb ≥ 9 gm/dl
- Calculated creatinine clearance must be ≥ 30 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - age)(weight\ in\ kg)}{(72)(serum\ creatinine\ in\ mg/dL)}$

Creatinine clearance for females = $\frac{(140 - age)(weight\ in\ kg)(0.85)}{(72)(serum\ creatinine\ in\ mg/dL)}$

3.15 ECOG Performance Status (PS 0, 1, 2) (Appendix I).

3.16 Ability to provide informed written consent.

3.17 Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.18 Life expectancy ≥ 6 months.

3.19 Negative serum pregnancy test done ≤ 14 days prior to registration, for women of childbearing potential only.

3.2 Registration - Exclusion criteria

3.21 Patients with locally advanced unresectable (T4b) or metastatic urothelial carcinoma (N1M0-1) as assessed on baseline radiographic imaging obtained ≤ 70 days prior to study registration. The required radiographic imaging includes:

- Abdomen/Pelvis CT or MRI scan
- Chest x-ray or CT scan

3.22 Patients with concurrent urothelial carcinoma and/or related variants anywhere outside bladder

NOTE: Patients with history of non-invasive (Ta, Tis) upper tract urothelial carcinoma that has been definitively treated with at least one post-treatment disease assessment (i.e. cytology, biopsy, imaging) that demonstrates no evidence of residual disease are eligible.

3.23 A prior or concurrent malignancy of any other site or histology unless the patient has been disease-free for > 2 years prior to registration except for:

- non-melanoma skin cancer and/or localized prostate cancer(T2 a or b , Gleason <3+4) or carcinoma *in situ* of the uterine cervix which has been adequately treated ≤2 years prior to registration
- or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score ≤ 3+4, and prostate-specific antigen [PSA] ≤ 10 mg/mL, etc.)

3.24 Patients who have received the last administration of an anti-cancer therapy including chemotherapy, immunotherapy, and monoclonal antibodies ≤ 4 weeks prior to registration, or who have not recovered from the side effects of such therapy.

EXCEPTION: Except single dose intravesical chemotherapy administered after TURBT.

3.25 Patients who have received prior therapy with immune checkpoint inhibitors (e.g. anti-PD-1, anti-PD-L1, anti-LAG3, anti-CTLA-4, anti-TIM3) or immune costimulatory molecules (e.g. anti-CD137, anti-OX40, anti-GITR) directed agents.

3.26 Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to registration, or who have not recovered from side effects of such procedure or injury prior to registration.

NOTE: Patients who have had minor procedures (i.e. TURBT) or percutaneous biopsies prior to registration are eligible.

3.27 Patients with history of cirrhosis, alcoholic or non-alcoholic steatohepatitis (NASH), auto-immune hepatitis, or previous grade 3-4 drug-related hepatitis.

3.28 Patient with history of prior solid organ or allogeneic bone marrow transplant.

3.29 Clinically significant cardiac diseases, including any of the following:

- History or presence of serious uncontrolled ventricular arrhythmias
- Clinically significant resting bradycardia
- Any of the following ≤ 3 months prior to registration: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)

- Uncontrolled hypertension defined by a SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg, with or without anti-hypertensive medication(s)

3.29a History of untreated HIV

NOTE: There is no requirement to screen patients for HIV. Patient with history of HIV infection are allowed if on effective HAART therapy and CD4 count more than 250.

3.29b History of active hepatitis B infection

NOTE: There is no requirement to screen patients for hepatitis B

3.29c History of active hepatitis C infection

NOTE: There is no requirement to screen patients for hepatitis C

3.29d Known diagnosis of any condition (i.e. post-hematopoietic or organ transplant, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc.) that requires chronic immunosuppressive therapy.

NOTE: Usage of non-steroidal anti-inflammatory medications (NSAIDS) for the treatment of osteoarthritis and uric acid synthesis inhibitors for the treatment of gout are permitted. For questions, please consult the study chair.

3.29e Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol

3.29f Pregnant or breast-feeding women

3.29g Women of child-bearing potential, who are biologically able to conceive, and not employing two forms of highly effective contraception. Highly effective contraception must be used throughout the trial and up to 8 weeks after the last dose of study drug (e.g. male condom with spermicidal; diaphragm with spermicide; intra-uterine device). Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 14 days prior to registration.

3.29h Fertile males not willing to use contraception, as stated above

3.29i Patients unwilling or unable to comply with the protocol

3.29j Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.29k Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5.0 Grade ≥ 3)

4.0 Test Schedule

			Active Monitoring Phase							
Tests and procedures	**≤70 days prior to reg**	**Screening (≤28 days prior to reg)**	**C1 (D1)**	**C2 (D15)**	**C3 (D29)**	**C4-C10 (D43, D57, D71, D85, D99, D113, D127)**	**End of Treatment (30 days after last dose)**	**6 Mo after registration (Clinical Follow-up)**	**9 Mo after registration (Clinical Follow-up)**	**EOS (12 Mo after registration) (Clinical Follow-up)**
Window				±3 days	±3 days	±3 days	±3 days	±14 days	±14 days	±14 days
Maximal TURBT/EUA	X									
History and Physical Exam		X		X	X	X	X	X	X	X
Vital Signs, Weight and ECOG PS		X	X	X	X	X	X	X	X	X
Height		X								
Pregnancy test (serum)		X[1]								
Pregnancy test (urine)[1]				X	X	X				
Adverse event assessment/ Toxicity notation[4]		X	X	X	X	X	X	X	X	X
Conmeds		X	X	X	X	X	X	X	X	X
Disease assessment: CT/MRI abdomen/ pelvis[8]	X					X[3]		X	X	X
Chest CT[8]	X					X[3]		X	X	X
ECG_R	X									
Hematology[2]		X		X	X	X	X	X	X	X

			Active Monitoring Phase							
Tests and procedures	**≤70 days prior to reg**	**Screening (≤28 days prior to reg)**	**C1 (D1)**	**C2 (D15)**	**C3 (D29)**	**C4-C10 (D43, D57, D71, D85, D99, D113, D127)**	**End of Treatment (30 days after last dose)**	**6 Mo after registration (Clinical Follow-up)**	**9 Mo after registration (Clinical Follow-up)**	**EOS (12 Mo after registration) (Clinical Follow-up)**
Window				±3 days	±3 days	±3 days	±3 days	±14 days	±14 days	±14 days
Blood-chemistries[6]		X		X	X	X	X	X	X	X
Free T4 and TSH		X				X[7]	X[7]			X[7]
Urine cytology		X						X	X	X
Urodynamic study	X[5]									X R
Bladder Biopsy	X							X		
Cystoscopy	X							X	X	X
QOL forms[11]		X					X			X
Optional Research specimens per IRB 16-005260[9]										
Optional Archived research tissue specimens [10,R]										

Cycle = 14 days All tests and procedures are clinically indicated, unless noted with an R to indicate funding by research

1. For women of childbearing potential only. Serum must be performed ≤14 days prior to registration
2. CBC with differential
3. Abdomen, pelvis, chest CT/MRI to be done at C7(Day 85) +/- 7 days
4. Adverse event/Toxicity notation to be done **WEEKLY** during radiation treatment
5. Uroflow/post void residual; not required to be done prior to registration; however, if done then data will be collected. .
6. Blood chemistries: Comprehensive Metabolic Panel (CMP) {Albumin, Bilirubin(total), Calcium, Carbon dioxide

(bicarbonate), Chloride, Creatinine, Glucose, Phosphatase alkaline, Potassium, Protein (total), Sodium, Transferase aspartate amino(AST) (SGOT), Transferese alanine amino (ALT) (SGPT), Urea nitrogen (BUN} and Mg prior to each avelumab dose, at end of study visit, and 30 days post-treatment safety follow-up

7. Free T4 and TSH at least every 8 weeks during treatment (Collect at same time as treatment related labs). Also collect at end of study or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks)
8. With contrast preferred; however if treating Provider determines that contrast is contraindicated then contrast can be omitted.
9. NOTE: Participants sign a separate consent for IRB 16-005260
10. Archived tissue per section 17.0
11. EORTC QLQ-C30 (Appendix II) and EORTC QLQ-BLM30 (Appendix III). Booklets are to be used for this study.

R Research funded (see Section 19.0)

4.1 Survival Follow-up

This study does not involve survival follow-up. Patients are considered off study 12 months after registration.

5.0 Grouping Factor:

Study Stage: 1=Safety Run-in vs 2=Expansion portion

6.0 Registration Procedures

6.1 Safety Run-In

Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] to insure that a place on the protocol is open to the patient.

To register a patient, fax ([redacted]) a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Registration, following the completion of run-in portion:

6.21 Registering a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted]) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.3 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.5 Correlative Research

6.42 Optional

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 17.0).

- Patient has/has not given permission to give his/her tissue sample for research testing.

6.6 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist or radiation oncologist

6.7 Treatment start

Treatment cannot begin prior to registration and must begin ≤7 days after registration.

6.8 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.9a Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9b A radiation oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

6.9c Study drug

Study drug is available on site.

6.9d Patient questionnaire booklets

Patient questionnaire booklets are available on site. Copies are not acceptable for these submissions. Booklets should be ordered using the Patient Questionnaire Order Form

6.9e Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

Safety Run-in

The first 6 patients enrolled will be included in the safety run-in portion following the treatment schedule included below (section 7.1). Patients will be treated for the first two cycles with avelumab only. Chemoradiation will begin at cycle 3 (Day 29). This will be performed to determine whether or not the proposed concurrent chemotherapy radiation treatment combined with avelumab is a safe regimen. ACCRUAL WILL BE TEMPORARILY HALTED between the safety run-in and expansion portion in order to evaluate the concurrent radiation therapy adverse event data. This data will be reviewed by the Study Chair and Study Statistician.

7.1 Treatment Schedule

7.11 Drug Treatment schedule - Use actual weight or estimated dry weight if fluid retention. Chemotherapy choice is based on treating provider's discretion.

7.12 For both cohorts: Avelumab 10mg/kg doses prior to initiation of concurrent chemo-radiation therapy. The treatment will continue for 10 total doses.

7.13 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 10mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Patients must be observed for 30 mins post avelumab infusion for potential related reactions

7.14 Premedication

Premedicate patients with an antihistamine and with acetaminophen

(acetaminophen 650 mg) PO and diphenhydramine 25-50 mg PO x 1 prior to the first 4 infusions of avelumab. Premedication

should be administered for subsequent avelumab doses based upon clinical judgement and presence/severity of prior infusion reactions.

7.15 Treatment Medication safety run-in and expansion portions

NOTE: cohort selection is treating provider's choice

Cohort	*Agent*	*Dose*	*Route*	*Day*	*Infusion time*
1 & 2	Avelumab	10mg/kg	IV	Q2weeks for a total of 10doses(cycles)	Over 60 minutes (+/- 10minutes)
1	5-FU	500 mg/m2/day	Continuous IV infusion via ambulatory pump	Day1-5 and Day 16-20 of RT. Please note that the infusion is based on day on RT.	Per standard of care
1	Mitomycin C	12 mg/m2	IV push	1 cycle only. Starting on C3D1(Day 29)	N/A
2	Cisplatin	35 mg/m2/day	IV	Starting on C3-5,D1(Day 29) and continue weekly for up to 6 weeks. If hypofractionated RT is used then cisplatin will finish early.	Per standard of care

NOTE: cohort selection is treating provider's choice

A maximum of 2 doses of 5-FU and one dose of mitomycin (MMC) or 6 weekly cycles of cisplatin will be administered based on the above schedule. A maximum of 10 cycles of avelumab immunotherapy will be administered in both Cohort 1 and Cohort 2. If a hypofractionated schedule of RT is used then cisplatin therapy will be stopped early with completion of RT.

Dosage for all the chemotherapy and immunotherapy regimens is based on approved FDA dosing schedules.

All cycles will be based on avelumab given once every 14 days.
Chemo and radiation therapy may be given as clinically indicated and any delays are per treating provider's discretion. Such delays do not affect the cycle length of avelumab.

Patients must be observed for 30 mins post avelumab infusion for potential related reactions.

Avelumab dosing:

To account for drug quantities supplied within each vial and to minimize wasted unused investigational drug, pharmacy may adjust the calculated drug dose +/- 10% for each patient. All patients dosed within these parameters will be considered dosed at full dose.

Definition of an Overdose for Avelumab used in this protocol:

Patients dosed > 10% above their calculated drug dose will be considered over-dosed.

7.2 Radiation Therapy

NOTE: Protocol defined radiation treatment is planned to begin at C3D1 (D29 of overall study) (+/- 7 days)

NOTE: Protocol radiation simulation can begin before or after registration in anticipation to start radiation C3D1 (D29 of overall study) (+/- 7 days)

7.21 Radiation Dose

7.211 Doses throughout will be prescribed in Gy for the IMRT. Total dose will be 64 Gy (in 2 Gy; or 55 Gy in 2.75Gy(RBE)/Gy, for 5 fractions per week. The D95% of the PTV1 should receive the prescription dose. The minimum dose to the OTV1 or PTV1 should be 90% of the prescription dose.

7.212 For prescription purposes D95% of the PTV2 shall receive ≥80% of the prescription. Minimum dose to the PTV2 or OTV 2 will be >70% of the prescription.

7.213 Prescription dose to the PTV shall be according to the following schema delivered in 2 Gy per fraction or 2.75 Gy per fraction. in consecutive fractions Monday-Friday for a total of 20 treatments or 32 treatments based on the radiation regimen chosen by the physician.

7.215 Volumes:

- CTV 1= GTV including intra-vesical or extra-vesical tumor + tumor bed resection area.
- PTV 1= CTV1+8mm
- CTV 2 = CTV 1 + bladder + bladder neck
- PTV 2= CTV 2 +8mm

7.22 Equipment and Physical Factors

Radiation will be delivered using the available x-ray equipment

7.23 Localization and Imaging Requirements

- Localization: Proper localization of the appropriate target volumes requires reproducible immobilization and correlation of imaging studies. Planning CT scans will be performed using a high-resolution scanner with ≤ 2 mm cuts through the region of interest (bladder), and at least 5mm elsewhere in the pelvis. MRI will also be considered appropriate for structures' definition.

MRI of the pelvis and bladder can be used for treatment planning volume delineation. T2 sequence 3D with ≤ 2mm spacing is recommended.

If PET scan was done prior to the TURBT it can be used to help define the CTV1.

- Immobilization: Patients will be immobilized for the treatment in a supine or prone position, using an appropriately customized immobilization device.

- Treatment: Patients will be encouraged to undergo treatment with an empty bladder and an empty bowel. Close fitting devices as used for simulation will be used for daily treatments.

Daily position verification: Patients will be setup with lasers in a custom fitting device. Patient orientation will be verified based on skin marks. Daily bladder position will then be verified based on volumetric guidance employing the techniques described below.

7.24 On-line Daily Correction

We do realize that for an individual patient bladder movement and set up error may be non-parametric and a large random component may be present. Thus, several different **volumetric image guidance modalities** may be used.

7.25 Error Verification

- 3D volumetric guidance: cone beam CT, CT on rails, MRI, or other means of 3D guidance can be employed.

7.25 Critical Normal Structures

- Gross tumor volume: will include any intravescal or extravesical tumor

- Clinical Target Volume.

CTV1: It would consist of GTV + tumor bed. All imaging modalities and information available should be used to define the extend of the disease. If not clinically contraindicated an MRI T2 cube can be used to aid define the gross tumor volume and resection area (tumor bed).
CTV2: It would consist of CTV1 + bladder + bladder neck
Rectum: is defined from the ischial tuberosities to the sigmoid flexure.
Small bowel: is defined by the small bowel in contact with the bladder. It should be contoured including 2 cm above the treatment field

7.27 Normal Tissue Constraints (NTC)

Normal tissue constraints (NTC) to define dose.

Table 2a. Standard-fractionation

Structure	Constraint	Minor deviation	Major deviation
PTV1	D95%=100	<99%	<96%
	Min >90%	<90%	<85%
	Dmax <108%	>108%	>110%
PTV 2	D95=≥80%	<80%	<75%
	Min >70%	<70%	<65%
Rectum	V90% <35%		
Femoral heads	V45 <1 cc	V45 <2 cc	V45 ≥ 2cc
Small bowel	Dmax <105%		
	100% <10cc		

- The maximum dose without a major deviation will be used for treatment.
- Normal tissue volumes
- Rectum: is defined inferiorly from the ischial tuberosities and superiorly to the sigmoid flexure.
- Small bowel: Individual loops should be contoured including 3 cm above and below the target or targets.
- Femoral Heads: Countered to the level of the lesser trochanter.

7.28 Quality Assurance (Physics check)

- Physicist team at each site is responsible for quality assurance. This is per standard of care
- Daily online volumetric imaging will be used. Soft tissue matching will be done. If fiducials are available they can be used to as a verification aid.
- Coronal, transverse, and sagittal CT slices with overlaid doses representing the total dose to be delivered should be available.
- Dose volume histograms (DVH) including, but not limited to, bladder, bladder wall, femoral heads, and rectal wall will be available.
- If available, different imaging and biologic-imaging studies can be used to define different structures. DVH will be performed as needed.

7.29a Treatment Interruptions

Treatment should be delivered over 20 or 32 consecutive treatments. Unplanned interruptions, consecutive or not, for more than 5 treatment days (Monday-Friday) are not allowed. Treatment breaks ≥ 5 days are considered major deviations and not allowed. If treatment interruptions of 5 days or longer are not of medical necessity, arrangements To

continue treatment should be done. Major treatment deviations will not exclude patient from the trial or for data analysis.

Treatments should be planned to be delivered on consecutive days, Monday to Friday.

7.29b Radiation Toxicity

The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 from the National Cancer Institute (NCI) will be used for toxicity grading. All patients will be seen weekly by the radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential side effects:

- Rectal irritation manifesting as diarrhea, rectal incontinence, proctitis or rectal bleeding.
- Bladder toxicity including urinary frequency/urgency, dysuria, hematuria, obstruction, retention and incontinence.
- Presence or absence of erections sufficient for sexual activity and use of medications or mechanical aids to enhance erections should be recorded.

Clinical discretion may be exercised to treat side effects from radiation therapy.

8.0 Dosage Modification Based on Adverse Events

The following modifications are suggestions but the treating provider is advised to use clinical judgement in dose modifications keeping in mind safety of the patients.

Dose Limiting Toxicity Definition

While dose limiting toxicity (DLT) is commonly defined by specified toxicities that occur during cycle 1 of therapy, within this trial the timeframe for DLT evaluation will include the entire duration of CRT therapy (date of first radiation fraction administration to date of last radiation fraction administration) to coincide with completion of a standard bladder-sparing CMT schedule in which radiation is administered once daily during weekdays for 20-32 fractions (treatments).

As standard bladder-sparing CMT is known to produce grade 1-2 TRAEs in nearly all patients and grade 3-4 Treatment-related adverse events (TRAEs) in 35% of patients, treatment related toxicity is expected [2, 4]. With standard CMT, however, immune related adverse events (irAEs) are not observed. Therefore, in evaluating safety of the new avelumab containing CMT treatment approaches within this protocol, severe irAEs or non-immune TRAEs which compromise the ability to deliver CMT are of particular interest. Accordingly, DLT **during the safety run-in portion of the protocol will be defined as the following:**

a) Prolonged grade 2 (lasting more than 21 days) or higher irAEs including (hypophysitis, uveitis, , hepatitis, and colitis).

NOTE: Treatment related hypothyroidism that is successfully treated with levothyroxine oral supplementation and does not cause a treatment delay in radiation by > 21 days is not considered a DLT event. In the case of suspected irAEs, diagnostic confirmation (supporting labs, imaging, biopsies, etc.) should be provided in all reports.

b) Grade 2 or higher non-immune TRAEs which cause a delay in radiation therapy by > 21 days.

c) Any grade myocarditis

d) Grade 2 pneumonitis

ALERT: ***ADR reporting may be required for some adverse events (See Section 10.0)*** ←

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2* and 8.3)

Dose Level	***Cisplatin*** **	***5-FU*****	***Mitomycin*****	**Avelumab**
1*	35mg/m2	500mg/m2	12mg/m2	10 mg/m2
-1	28mg/m2	400mg/m2	No dose reductions	No dose reductions
-2	20mg/m2	No dose reductions	No dose reductions	No dose reductions

*Dose level 1 refers to the starting dose.

**Cisplatin, 5-FU, Mitomycin: these are suggested dose levels and are only a guideline

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified*** ← ←

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

General guidance for dose modifications and treatment delays and discontinuation

Due to the prolonged half-life associated with monoclonal antibodies, no dose reductions of avelumab are planned.

If participant has any grade 3 toxicity with the chemotherapy or immunotherapy, radiation can still continue if considered safe by the treating provider. If all therapy is stopped including chemotherapy, immunotherapy and radiation then patient will be followed as per the routine follow up for one year.

8.2 Dose Modification Guidelines for Drug-Related Adverse Events for Avelumab

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

NOTE: If anvelumab therapy is delayed for more than 28 days then discontinue avelumab therapy

CTCAE System/Organ/Class (SOC)	ADVERSE EVENTS/SYMPTOMS	Avelumab
Gastrointestinal Disorders	**Diarrhea/Colitis** Grade 1	Continue and initiate supportive care per Section 9.0
	Diarrhea/Colitis Grade 2	Delay avelumab therapy If improves to Grade ≤ 1: Resume avelumab therapy **During radiation therapy:** If persists > 5-7 days or recurs: Treat as Grade 3 or 4. **Outside radiation therapy:** If persists > 14 days or recurs Discontinue avelumab. Continue and initiate supportive care per Section 9.0
	Diarrhea/Colitis Grade 3 to 4	Delay avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. Continue and initiate supportive care per Section 9.0 If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Skin and subcutaneous tissue disorders	**Rash acneiform** Grade 1 to 2	Continue and initiate supportive care per Section 9.0 If persists > 1 to 2 weeks or recurs: Delay avelumab therapy Consider skin biopsy Consider 0.5-1mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and **resume avelumab therapy following steroids taper.** If worsens: Treat as Grade 3 to 4.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENTS/SYMPTOMS	Avelumab
	Rash acneiform Grade 3 to 4	Delay avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections **If Grade 3 improves to Grade ≤ 1:** Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
	Rash maculo-papular Grade 1 to 2	If persists > 1 to 2 weeks or recurs: Delay avelumab therapy Consider skin biopsy Consider 0.5-1 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, **and resume avelumab therapy following steroids taper.** If worsens: Treat as Grade 3 to 4.
	Rash maculo-papular Grade 3 to 4	Delay avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections **If Grade 3 improves to Grade ≤ 1:** Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
General disorders and administration site conditions	**Infusion-related reaction** Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening
	Infusion-related reaction Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, iv fluids); prophylactic medications indicated for ≤ 24 h	• Temporarily discontinue avelumab infusion • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from avelumab treatment.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENTS/SYMPTOMS	Avelumab
	Infusion-related reaction Grade 3 or Grade 4 • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae • Grade 4: Life-threatening consequences; urgent intervention indicated	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment • All Grade 3 or 4 infusion reactions should be reported within 24 hours to EMD Serono and reported as an SAE if criteria are met.
Investigations	**Aspartate aminotransferase increased** or **Alanine aminotransferase increased** **Bilirubin increased** **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.
	Aspartate aminotransferase increased or **Alanine aminotransferase increased** **Bilirubin increased** **Grade 2** AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days. If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
	Aspartate aminotransferase increased or **Alanine aminotransferase increased** **Bilirubin increased** **Grade 3 to 4** AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted
	Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENTS/SYMPTOMS	Avelumab
	Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days Continue and initiate supportive care per Section 9.0 Consider renal biopsy If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
	Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1 to 2 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 disorders	**Myocarditis** 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.	Permanently discontinue avelumab.
	Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections. Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
Respiratory, thoracic and mediastinal disorders	**Pneumonitis** Grade 1	Consider delaying 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.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENTS/SYMPTOMS	Avelumab
	Pneumonitis Grade 2 or higher	Permanently discontinue avelumab therapy. Pulmonary and Infectious Disease consults. Continue and initiate supportive care per Section 9.0
Endocrine Disorders	**Grade 1 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)**	Continue avelumab therapy Endocrinology consult if needed Continue and initiate supportive care per Section 9.0 Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis) Follow-up Management: Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
	Grade 2, Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus) **Grade 2, Grade 3 or Grade 4 hypopituitarism/Hypophysitis (secondary endocrinopathies)**	Permanently discontinue avelumab therapy For Grade 3 or 4 consider hospitalization Endocrinology consult If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated
Other Immune Related Adverse Events (irAEs) (not described above)	**Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE**	Delay avelumab therapy pending clinical investigation If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
	Grade 2 irAE or first occurrence of Grade 3 irAE	Delay avelumab therapy 1 to 2 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.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENTS/SYMPTOMS	Avelumab
	Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2 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 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult. If improves to Grade ≤ 1: Taper steroids over at least 1 month
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	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.

NOTE: If anvelumab therapy is delayed for more than 28 days then discontinue avelumab therapy

Since inhibition of PD-L1 stimulates the immune system, **irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):**

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

8.3 Dose Modifications for Cisplatin, 5-FU, and/or Mitomycin (Based on Interval Adverse Events (occurring within a cycle of treatment)

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. This evaluation will monitor for adverse events (all grades), serious adverse events, immune related adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Concurrent chemo radiation is not expected to cause any immune related side effects. But since the therapy is being combined with avelumab which can induce immune related side effects if treating provider assessed an adverse event as immune related then it is recommended to perform appropriate work up and confirming the nature of side effect.

It is expected to observe grade 3-4 gastrointestinal and genitourinary side effects with concurrent chemo radiation. Symptom management as per best practices is recommended. It's appropriate to use growth factors for neutropenic complications.

CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT[a]**	**ACTION**
Blood and lymphatic disorders	Febrile neutropenia (fever without clinically or microbiologically documented infection) [ANC <1.0 X 10^9 C/L] fever ≥38.3°C)	Cisplatin , 5FU	Delay chemotherapy by 1 week until ANC recovers to Grade 0-2 and until fever resolves. Reduce dose by one level or more for subsequent cycles.
Cardiac Disorders	Left ventricular systolic Dysfunction, myocardial infarction	Cisplatin , 5FU	Grade 3 or higher hold chemotherapy until recovers to grade ≤1. .
Gastrointestinal disorders	Vomiting ≥Grade 3	Cisplatin , 5FU	If not controlled with optimal medication. Reduce dose by one dose level and use reduced level for subsequent cycles
Immune system disorders	Allergic reaction Grade 1 (eg, mild flushing, rash, pruritis)	Cisplatin , 5FU or Mitomycin	Stop infusion. After recovery restart the infusion as per standard of care
	Allergic reaction Grade 2-3 (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	Cisplatin , 5FU or Mitomycin	Stop infusion. Give IV antihistamine (diphenhydramine 50 mg IV), IV H2-receptor antagonist (famotidine 20 mg IV) and steroid (dexamethasone 10 mg IV) After recovery of symptoms resume chemotherapy as per standard of care

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT[a]	ACTION
	Anaphylaxis (e.g. one or more of the following): respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	Cisplatin, 5FU or Mitomycin	Stop infusion. give IV antihistamine (diphenhydramine 50 mg IV), IV H2-receptor antagonist (famotidine 20 mg IV) and steroid (dexamethasone 10 mg IV) Add epinephrine or bronchodilators if indicated, report as an adverse event Discontinue chemotherapy.
Investigations	Neutrophil count decreased ≥Grade 3 (ANC 500 to <1000/mm^3)	Cisplatin, 5FU	Delay chemotherapy by 1 week until recovery to Grade 0-2 Consider reducing dose by one level. Use of growth factors is allowed.
	Platelet count decreased ≥Grade 2 (<75 x 10^9/L)	Cisplatin, 5FU	Delay chemotherapy by 1 week until recovery to Grade 1. Consider reducing dose by dose 20% for subsequent cycles
Investigations	Bleeding ≥Grade 3 or requiring ≥2 platelet transfusions	Cisplatin , 5FU	Delay chemotherapy by 1 week until bleeding recovers to Grade 0-1 Permanently discontinue chemotherapy, or reduce dose by 20% or more for subsequent cycles
Nervous system disorders	Peripheral motor neuropathy Grade 2	Cisplatin	Reduce dose by 20% and use reduced level for subsequent cycles
	Peripheral motor neuropathy Grade 3 or higher	Cisplatin	Discontinue cisplatin
All other non-hematologic[b]	≥Grade 3	Cisplatin, 5FU	Discontinue chemotherapy, or reduce dose by 20% or more and use reduced dose for subsequent cycles
Nephrotoxicity	GFR <50 ml/min, first event	Cisplatin	Hold therapy till it recovers above 50ml/min and restart at one dose level lower or more if GFR goes down further. If Patient GFR falls below 50ml/min even with second dose reduction then omit cisplatin and continue with RT alone.

[a] If a drug is held, omitted, discontinued or dose-reduced, it is the treating provider's discretion to apply the modification to one or both cytotoxic drugs, and the decision should depend on the nature and severity of the particular adverse event and its likely causal relation to the agent.

[b] For adverse effects ≥Grade 3 commonly associated with radiation such as radiation dermatitis, dry mouth, mucositis, thick secretions/saliva, loss of taste, weight loss, loss of appetite dose modifications for chemotherapy will be at the discretion of the treating provider.

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating provider, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data. Patients can also continue with RT alone without chemotherapy if the treating provider chooses to hold chemotherapy.

Treatment at reduced dosage will be administered once the adverse event has come down to grade 1 or less

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti -inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to avelumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 8.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology 2015;33(28):3199-3212.

9.21 Neutropenia

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

9.22 Anemia

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

9.23 Thrombocytopenia

Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

9.3 Anti-infectives

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

9.4 Corticosteroids

Patients may continue on steroid inhalation therapy. Systemic corticosteroids are known immunosuppressive agents that can mitigate the effects of avelumab. Steroids should be generally reserved to treat side effects of avelumab. Steroids can be used as primary prevention of nausea per institutional guidelines, but steroid doses should be reduced in subsequent cycles if nausea/vomiting is absent or very mild (see Section 9.5).

9.5 Antiemetics

Antiemetics may be used at the discretion of the attending physician. Nausea and vomiting should be treated aggressively, and consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. Volume depletion should be corrected before initiation of study drug. Study team strongly recommends use of dexamethasone to be restricted to 4 mg once a week. We strongly recommend using long acting 5HT-3 inhibitors like palonosetrone and Nk1 inhibitor like fosprepitant or olanzapine to avoid delayed nausea esp. with cisplatin.

9.6 Anti-diarrheals

Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. (See Section 9.7 for management of treatment-related enterocolitis)

All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

NOTE: Loperamide/diphenoxylate/atropines should NOT be used for diarrhea symptoms unless: (1) it is believed that avelumab-related enterocolitis is unlikely to be present after detailed evaluation by gastroenterology, including endoscopy; PLUS (2) approval is documented by a gastroenterology specialist.

9.7 Immunotherapy-related toxicities

Patients should be monitored for signs and symptoms of immunotherapy-related toxicities, which include but are not limited to the following:

- **Pneumonitis**
  - For Grade 2 events, treat with systemic corticosteroids (1.0 to 2.0 mg/kg/day prednisone

or equivalent).
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids (1.0 to 2.0 mg/kg/day prednisone or equivalent). Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/colitis**
  Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For Grade 2 diarrhea/colitis, administer oral corticosteroids and antidiarrheals.
  - For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids (1.0 to 2.0 mg/kg/day prednisone IV or equivalent). Add prophylactic antibiotics for opportunistic infections.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  For **T1DM** or **Grade 3-4** Hyperglycemia:
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or hypothyroidism**
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids (1 to 2mg/kg/day prednisone or equivalent.) Add prophylactic antibiotics for opportunistic infections
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal failure or nephritis**
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.8 Management of treatment related enterocolitis

In patients with severe enterocolitis, avelumab will be held and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In patients with moderate enterocolitis, avelumab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

9.9a Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary treating provider.

9.91 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the case report forms (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 10.

9.92 Prohibited Concomitant Medications

The following medications are **not** permitted during the screening and treatment phase (including retreatment for post-complete response relapse) of this trial:

- Anti-neoplastic systemic cytotoxic chemotherapy or biological therapy outside the clinical trial program
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than avelumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the principal investigator.

NOTE: Use of steroids during chemoradiation for controlling chemotherapy-associated is allowed. We recommend only using up to 4mg dexamethasone weekly.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

9.9b Contraception

Avelumab may have adverse effects on a fetus in utero. Furthermore, it is not known if avelumab has transient adverse effects on the composition of sperm.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity. Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with avelumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Mayo Clinic and to EMD Serono without delay and within 24 hours to Mayo Clinic and within 2 working days to EMD Serono if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Mayo Clinic and to EMD Serono and followed as described above.

9.9c Use in Nursing Adults

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment. Specific additional information follows for individual agents used in this trial.

9.9c1 Avelumab

It is unknown whether avelumab is excreted in human milk. It is recommend that nursing mothers not to breast feed for at least one month after final dose.

9.9c2 Chemotherapy

Cisplatin has been reported to be found in human milk; patients receiving cisplatin injection should not breast-feed. It is not known if fluorouracil is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue fluorouracil, taking into account the importance of treatment to the mother.

It is not known if mitomycin is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer.

Table 6. Pretreatment Medication

Agent	*Dose*	*Route*	*Day*
DXM	*4mg*	*IV or PO*	*Prior to weekly cisplatin infusions*
Emend	*150 mg*	*IV*	*Prior to weekly Cisplatin infusions*
Palonosetron	*0.25mg*	*IV*	*Prior to weekly Cisplatin infusions*
Ondansetron	*8 mg*	*IV*	*C3D1 (Day 29) of Mitomycin + 5-FU infusion*
Prochlorperazine	*10 mg*	*PO*	*Prior to 5-FU infusion (~Day 50)*

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form [redacted] Will automatically be sent to [redacted] Non Mayo sites – complete and forward to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted]	Will automatically be sent to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted] AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to [redacted]

Definitions

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

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

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

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug

under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
General disorders and administration site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Skin and subcutaneous tissue disorders	Rash	≤Grade 4
	Erythema	≤Grade3
Gastrointestinal disorders	Colitis	≤Grade 3
	Nausea	≤Grade 3
	Vomiting	≤Grade 3
Renal and urinary disorders	Cystitis	≤Grade3
Injury, poisoning and procedural complications	Radiation dermatitis	≤Grade 3
Blood and lymphatic system disorder	Anemia	≤Grade 4
Respiratory, thoracic and mediastinal disorders	Pneumonitis	≤Grade 3

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

See section 10,8 for submission requirements to EMD Serono.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the Reportable Event coversheet and appropriate documentation to [redacted]. The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her treating provider. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.

Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
General disorders and administration site conditions	Pain	X	X
	Fatigue	X	X
Injury, poisoning and procedural complications	Dermatitis Radiation	X	X
Metabolism and nutrition disorders	Anorexia	X	X
Musculoskeletal and connective tissue disorders	Bone pain	X	X
Vascular disorders	Lymphedema	X	X
Respiratory, thoracic and mediastinal disorders	Pneumonitis	X	X
	Pulmonary fibrosis	X	X
Renal and urinary disorders	Hematuria	X	X

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
	Urinary frequency	X	X
	Urinary incontinence	X	X
	Urinary retention	X	X
	Urinary tract obstruction	X	X
	Urinary tract pain	X	X
	Urinary urgency	X	X
Gastrointestinal disorders	Number of stools	X	
	Diarrhea		X
	Constipation		X
	Fecal incontinence	X	X
	Nausea	X	X
	Proctitis	X	X
	Rectal hemorrhage	X	X
	Vomiting	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 EMD Serono - Additional Event Reporting Instructions

The following reportable events must be submitted to EMD Serono within 24 hours (or immediately for death or life-threatening events) using the applicable safety report form provided.

- 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: [redacted]
OR
E-mail [redacted]

Specifying:

- PROTOCOL Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

11.0 Treatment Evaluation

This study will not use RECIST criteria to evaluate response or progression. The patients enrolled will have nonmeasurable disease on imaging and response will be evaluated with biopsy or cytology at 6, 9 and 12 months post therapy.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 12 weeks after registration for the first year. The first 12 week evaluation will be a cross sectional imaging preferably same as done at the time of registration with CT or MRI of chest abdomen and pelvis. Patient subsequent 12 week assessment will include cross sectional imaging with office cystoscopy, cytology and biopsy (for cause).Biopsy of the tumor bed at 6 months is mandatory. Patient will also have routine blood work and translation and QOL assessments as described in the study table.

11.2 Criteria for evaluation and endpoint analysis.

a. Complete Response
Complete Response: Negative biopsy and negative urine cytology at 6 months from registration after finishing of concurrent RT and immunotherapy. Imaging of abdomen and pelvis confirming no systemic disease within 4 weeks of cystoscopy should be completed..

b. Progression
Progression**:** Progression in T stage, N stage or M stage both clinically or radiologically. Histological confirmation of metastatic disease is at the discretion of the treating provider.

c. Recurrence
Recurrence: histologically proven first appearance of muscle invasive bladder cancer, clinical evidence of metastatic disease, or treatment with radical cystectomy or radiation to the bladder, or death due to any cause after they were confirmed remission at 6 month evaluation .
   a. Event : Histologically proven presence of muscle invasive bladder cancer, clinical evidence of nodal or metastatic disease, radical cystectomy, death within 90 days of protocol specified treatment.

d. Performance Status
Performance Status: Patients will be graded according to the ECOG Performance Status Scale. (Appendix I)

12.0 Descriptive Factors*:*

12.1 Histology: pure urothelial vs mixed histology

12.2 Clinical T stage: T2 vs. T3 vs. T4

12.3 Cohort: cohort 1 (5-FU + Mitomycin C) versus cohort 2 (Cisplatin) chemotherapy
NOTE: cohort selection is treating provider's choice

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Those patients who have experienced unacceptable toxicity may be eligible for retreatment at a lower dose (see Section 8.0).

13.2 Off Study/Safety Follow-up Visit:

Patients should be evaluated for any residual toxicities, per test schedule section 4.0. For patients proceeding to cystectomy, this can coincide with traditional post-op visits. For patients who refuse to return to clinic for an in-person visit, recording of patient reported toxicities by telephone is acceptable.

13.3 Those patients who refuse further treatment will go off treatment and be withdrawn from the study.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the treating provider as long as there are no safety concerns, and the patient was properly registered. The patient will go or off study.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Clinical follow-up will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. The patient will be taken off study.

13.5 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient may continue treatment off-protocol at the discretion of the treating provider as long as there are no safety concerns, and the patient was properly registered.

13.6 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.7 Criteria for Removal from Study

Patients will be removed from the study for any of the following reasons:

- Completion of all study therapy and follow up.
- Patient non-compliance or request to withdraw from all therapy and follow up. Patients who withdraw from therapy only may continue to be followed for study specified follow up secondary endpoints.

- Pregnancy.
- Unacceptable toxicity that in the treating provider's discretion places the patient at risk for future significant harm.
- Intercurrent illness that prevents continuation of therapy or follow up.

14.0 Body Fluid Biospecimens

14.1 Collection and Processing

14.11 Optional research specimen(s) collection per protocol IRB 16-005260 will be done after consenting for 16-005260 and according to that protocol. All collection time points and processing will be done per that protocol. Data from IRB 16-005260 may be used for this study after IRB approval.

15.0 Drug Information

15.1 Avelumab (Bavencio®)

15.11 **Background**: Avelumab is a fully human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

15.12 **Formulation**: Avelumab is a sterile, clear, and colorless concentrate for solution available in a concentration of 20 mg/mL. Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).

15.13 **Preparation and storage**: Allow each vial to equilibrate to room temperature. Avelumab drug product must be diluted in 250 mL of 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used if needed. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles. No other drugs should be added to the solution for infusion containing avelumab.

Avelumab drug product must be stored at 2°C to 8°C until use. If not used immediately, the diluted drug product can be stored up to 8 hours at room temperature or up to 24 hours at 2°C to 8°C. Avelumab drug product must not be frozen.

15.14 **Administration:** Avelumab is administered as a 1-hour IV infusion. Administer the diluted solution through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron).

15.15 Pharmacokinetic **information**:
Absorption: Avelumab is administered intravenously and is 100% bioavailable. Steady-state concentrations of avelumab are expected to be

reached by the 3rd dosing cycle (10 mg/kg dose every 2 weeks), and the accumulation ration is 1.25.
Distribution: The geometric mean volume of distribution at steady state for a subject receiving 10 mg/kg was 4.72 L.
Metabolism: Avelumab is degraded by proteolytic catabolism. CYP450 does not contribute to its metabolism.
Elimination: The primary elimination mechanism of avelumab is proteolytic degradation. Based on population pharmacokinetic analyses in patients with solid tumors, the total systemic clearance was 0.59 L/day. The terminal half-life was 6.1 days in patients receiving 10 mg/kg every 2 weeks.

15.16 **Potential Drug Interactions**: Avelumab is not expected to have drug-drug interactions with other drugs because it is primarily metabolized through catabolic pathways and is not expected to affect the expression of CYP450 enzymes.

15.17 **Known potential toxicities**: Consult the package insert for the most current and complete information.

Very Common (≥ 10%): Anemia, nausea, diarrhea, vomiting, abdominal pain, fatigue, pyrexia, peripheral edema, infusion related reaction, weight decreased, decreased appetite, back pain, arthralgia, cough, dyspnea

Common (≥ 1% - < 10%): Hypothyroidism, chills, pneumonitis, rash, pruritus, rash maculopapular

Uncommon (≥ 0.1% - < 1%): Adrenal insufficiency, hyperthyroidism, thyroiditis, autoimmune thyroiditis, adrenocortical insufficiency acute, hypopituitarism, uveitis, colitis, autoimmune colitis, enterocolitis, autoimmune hepatitis, acute hepatic failure, hepatic failure, hepatitis, drug hypersensitivity, anaphylactic reaction, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, blood creatine phosphokinase increased, transaminases increased, diabetes mellitus, myositis, Guillian-Barré syndrome, tubulointerstitial nephritis, rash pruritic, erythema, rash generalized, rash erythematous, rash macular, rash papular, dermatitis exfoliative, erythema multiforme, pemphigoid, pruritis generalized.

Adverse reactions with observed fatal outcome in the avelumab clinical development programs included: immune-related pneumonitis, immune-related hepatitis, and immune-related myocarditis.

15.18 **Drug procurement:**
Investigational avelumab is provided free of charge to patients by EMD Serono a subsidiary of Merck KGaA. Outdated or remaining drug is to be destroyed on-site per procedures and local regulations in place at each institution.

15.19 **Nursing Guidelines:**
15.191 Avelumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening.

Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.193 Rash/pruirits/dermatitis is seen. Rarely Steven Johnson Syndrome has been seen and can be life threatening. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.194 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well" . Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.197 Patients who are started on steroid therapy for any side effects of avelumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.199 Other rare side effects include Guillian-Barre syndrome, nephritis, myocarditis, infusion reaction, and cytopenias. Instruct patients to report and side effects to the study team immediately.

15.2 Fluorouracil (Adrucil, Efudex, [5FU])

15.21 **Background**: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog). Fluorouracil is a fluorinated Pyrimidine Antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle.

15.22 **Formulation**: Commercially available for injection 50 mg/mL (10 mL, 20 mL, 50 mL, and 100 mL).

15.23 **Preparation, storage, and stability**: Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Dilute in 50 – 1000 mL of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil should not be coadministered with either diazepam, doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine. However, fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide.

15.24 **Administration:** Fluorouracil may be given IV push, IV infusion. Refer to section 7.0 (treatment) administration instructions specific to the protocol.

15.25 **Pharmacokinetic information**:
Distribution: V_d ~ 22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g., pleural effusions and ascitic fluid)
Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.
Half-life elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.
Excretion: Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours.

15.26 **Potential Drug Interactions**: Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation). Avoid black cohosh.

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.
Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.

Emetic potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg: Moderate (30% to 60%)
Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.
Local: Irritant chemotherapy.

Less common known potential toxicities, 1% - 10%:
Dermatologic: Dry skin
Gastrointestinal: GI ulceration

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization. Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Guidelines:**

15.291 Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

15. 292 Administer antiemetics as indicated.

15. 293 Diarrhea may be dose–limiting; encourage fluids and treat symptomatically.

15. 294 Assess for stomatitis; oral care measures as indicated. May try vitamin E oil dabbed on sore, six times daily. Cryotherapy recommended with IV push administration.

15. 295 Monitor for neurologic symptoms (headache, ataxia).

15. 296 Inform patient of potential alopecia.

15. 297 Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.

15.298 5FU–induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

15.299 Photosensitivity may occur. Instruct patients to wear sun block when outdoors.

15.3 Mitomycin (Mutamycin®):

15.31 **Background:** Mitomycin is an antitumor antibiotic that alkylates DNA to produce DNA cross-linking (primarily with guanine and cytosine pairs) and inhibits DNA and RNA synthesis. Mitomycin is not cell cycle specific but has its maximum effect against cells in the late G and early S phases.

15.32 **Formulation**: Commercially available for injection as:
Injection, solution reconstituted in 5 mg, 20 mg, and 40 mg vials.

15.33 **Preparation and storage**: Store intact, unreconstituted mitomycin at controlled room temperature and is stable for the lot life indicated on the package. Avoid excessive heat over 40 ºC. Reconstituted mitomycin with Sterile Water for Inject to a concentration of 0.5 mg/mL is stable for 14 days refrigerated or 7 days at room temperature. Protect reconstituted solution from light. Diluted mitomycin in various IV fluids at room temperature, a concentration of 20 to 40 micrograms/mL is stable as follows: in 5% Dextrose Injection – stable 3 hours, in 0.9% Sodium Chloride Injection – stable 12 hours, and in Sodium Lactate Injection – stable 24 hours. Administer IV push/bolus or via IV piggyback. Consider using a central venous catheter as mitomycin is a vesicant.

15.34 **Administration:** Administer by slow IV push/bolus via a freely-running saline infusion.

15.35 **Pharmacokinetic information**:
Metabolism: Primarily hepatic
Half-life elimination: 17 minutes (30 mg dose)
Excretion: Feces primarily; urine

15.36 **Potential Drug Interactions**:
Metabolism/Transport Effects: Substrate P-glycoprotein
Increased Effect/Toxicity: The levels/effects of mitomycin may be increased by P-glycoprotein/ABCB1 inhibitors, vinca alkaloids, denosumab, dipyrone, palifermin, pimecrolimus, ronalazine, roflumilast, trastuzumab.
Decreased Effect: The levels/effects of mitomycin may be decreased by Echinacea, Lumacaftor, P-glycoprotein/ABCB1 inducers.

15.37 **Known potential toxicities**: Consult the package insert for the most current and complete information. US Boxed Warnings include: Bone marrow suppression, hepatotoxicity, carcinogenic and teratogenic.

Common known potential toxicities, > 10%:
Gastrointestinal: Nausea, vomiting, anorexia
Hematologic & oncologic: Bone marrow depression, hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP)
Miscellaneous: Fever

Less common known potential toxicities, 1% - 10%:
Dermatologic: Alopecia
Gastrointestinal: Mucous membrane disease, stomatitis

Renal: Increased serum creatinine

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Adult respiratory distress syndrome (ARDS), bladder spasm (intravesical administration), cardiac failure, dyspnea, extravasation reactions, fibrosis (bladder; intravesical administration), hepatic sinusoidal obstruction syndrome (formerly known as hepatic veno-occlusive disease), interstitial fibrosis, malaise, nonproductive cough, pulmonary infiltrates, renal failure (irreversible), skin rash, weakness

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines:**

15.391 Administer antiemetics and antidiarrheals as needed.

15. 392 Monitor CBC and platelet count: Thrombocytopenia may be cumulative and dose–limiting. Instruct patient to report any signs or symptoms of infection, unusual bruising or bleeding to the health care team.

15. 393 Premedicate with antiemetics and assess for their effectiveness.

15. 394 Monitor for interstitial pneumonitis and pulmonary fibrosis which may respond to corticosteroid therapy.

15. 395 Fatigue is common. Educate patient to incorporate rest periods in daily routine.

15. 396 Monitor for signs of hemolytic uremic syndrome. Characterized by rapid fall in hemoglobin, renal failure (rise in creatinine), severe thrombocytopenia, with progression to pulmonary edema and hypotension. Assess creatinine before administration and hold dose and inform MD if crt. >1.7 mg/dl.

15.397 Mitomycin is a potent vesicant – avoid extravasation. Ensure patency of IV before and throughout administration. If extravasation occurs stop infusion and refer to your institutions treatment policy. Closely monitor skin for signs of tissue necrosis, erythema, and tissue sloughing.

15.398 Interstitial pneumonitis occurs rarely, but can be quite severe and lead to ARDS. Assess baseline pulmonary status at initiation of treatment and before subsequent cycles. Instruct patient to report any non-productive cough, dyspnea, hemoptysis, or chest pain.

15.4 Cisplatin (CDDP)

15.41 **Background**: Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases and disrupts DNA function; may also bind to proteins. Cisplatin can also bind two adjacent

guanines on the same strand of DNA producing intrastrand cross-linking and breakage.

15.42 **Formulation**: Commercially available for injection as:
Solution [preservative free]: 1 mg/mL (50 mL, 100 mL, 200 mL)

15.43 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Do not refrigerate solution, a precipitate may form. Further dilution stability is dependent on the chloride ion concentration and should be mixed in solutions of sodium chloride concentrations at least 0.3% NaCl. Further dilutions in 0.9% NaCl, D_5/0.45% NaCl, or D_5/0.9% NaCl to a concentration of 0.05-2 mg/mL are stable for 72 hours at 4ºC to 25ºC. The infusion solution should have a final sodium chloride concentration equal to or greater than 0.2% NaCl.

15.44 **Administration:** Refer to the treatment section for specific administration instructions. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Pretreatment hydration with 1-2 L of fluid is recommended prior to cisplatin administration; adequate hydration and urinary output (> 100 mL/hour) should be maintained for 24 hours after administration. Hydration may be accomplished by adding the appropriate dose of cisplatin to 750 mL 0.5 D5/0.45% NaCl with 25 grams of Mannitol (approximating 1000 mL final volume) and infused over 2 hours. The IV rate of administration has varied from a 15- to 120-minute infusion, 1 mg/minute infusion, 6- to 8-hour infusion, 24-hour infusion, or per protocol; maximum rate of infusion of 1 mg/minute in patients with CHF.

15.45 **Pharmacokinetic information:**
Distribution: Rapidly into tissue; high concentrations in kidneys, liver, ovaries, uterus, and lungs
Protein binding: >90%
Metabolism: Nonenzymatic; inactivated (in both cell and bloodstream) by sulfhydryl groups; covalently binds to glutathione and thiosulfate
Half-life elimination: Initial: 20-30 minutes; Beta: 60 minutes; Terminal: ~ 24 hours; Secondary half-life: 44-73 hours
Excretion: Urine (>90%); feces (10%)

15.46 **Potential Drug Interactions**:
Increased Effect/Toxicity: Delayed bleomycin elimination with decreased Glomerular filtration rate. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel).
Decreased Effect: Sodium thiosulfate and amifostine theoretically inactivate drug systemically; have been used clinically to reduce systemic toxicity with administration of cisplatin.

Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.47 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Central nervous system: Neurotoxicity: Peripheral neuropathy is dose- and duration-dependent
Dermatologic: Mild alopecia
Gastrointestinal: Nausea and vomiting
Hematologic: Anemia, leukopenia (nadir day 18-23, recovery by day 39, dose related), thrombocytopenia (nadir day 18-23, recovery by day 39, dose related)
Hepatic: Liver enzymes increased
Renal: Nephrotoxicity (acute renal failure and chronic renal insufficiency)
Otic: Ototoxicity, manifested as high frequency hearing loss; ototoxicity is especially pronounced in children

Less common known potential toxicities, 1% - 10%:
Local: Tissue irritation

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Alopecia, ageusia, anaphylaxis, aortic thrombosis, autonomic neuropathy, bradycardia, cardiac arrhythmia, cardiac failure, cerebrovascular accident, extravasation, hemolytic anemia (acute), hemolytic-uremic syndrome, hiccups, hypercholesterolemia, hyperuricemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, increased serum amylase, leukoencephalopathy, myocardial infarction, neutropenic enterocolitis, optic neuritis, pancreatitis, papilledema, peripheral ischemia (acute), phlebitis, SIADH, tachycardia, thrombotic thrombocytopenic purpura

15.48 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.49 **Nursing Guidelines:**

15.491 May react with aluminum IV set, forming a black precipitate and losing its potency.

15. 492 Assess laboratory values prior to drug administration, especially CBC, platelets, creatinine.

15. 493 Patient should be hydrated before administration. Stress post infusion hydration maintenance to reduce risk of nephrotoxicity.

15. 494 Administer aggressive antiemetic therapy pre- and post-treatment.

15.495 Monitor for signs of neurotoxicity and ototoxicity. Instruct patient to report any numbness, burning, or tingling in hands and feet to health care team. Also instruct patient to report any changes in hearing or ringing in the ears to health care team.

15.496 Monitor magnesium and potassium levels, and for signs and symptoms of hypomagnesemia and hypokalemia, supplements may be needed.

15.497 Instruct patient about alopecia.

15.498 Use cautiously with loop diuretics as these may increase the risk of ototoxicity.

15.499a Monitor for signs and symptoms of allergic reactions. Treat according to your institution's protocol.

15.499b Monitor renal function tests.

16.0 Statistical Considerations and Methodology

16.1 Overview: This protocol will assess the efficacy and safety of concurrent chemotherapy radiation treatment combined with avelumab in patients with muscle invasive bladder cancer using a two-stage Simon optimum design. A safety run-in with 6 patients (described in Section 7.0) will be conducted prior to the expansion portion.

A safety analysis will be conducted after 6 patients have been enrolled and have been treated for a minimum of three cycles. Patients will be treated for the first two cycles with avelumab only. Chemoradiation will begin at cycle 3 (Day 29).This will be performed to determine whether or not the proposed combination chemotherapy regimen + radiation therapy with avelumab is a safe regimen. ACCRUAL WILL BE TEMPORARILY HALTED between the safety run-in and expansion portion in order to evaluate the concurrent radiation therapy adverse event. This data will be reviewed by the Study Chair and Study Statistician. The adverse event stopping rule in Section 16.42 will be in effect for patients in the initial safety run-in portion as well as patients in the expansion portion (efficacy portion) of this study. If this regimen at the proposed dosages is deemed safe, these 6 patients will be considered the first 6 patients in this study. Adverse events will continue to be monitored for all subsequent patients per the adverse event stopping rule described in section 16.42.

16.11 Primary Endpoint: The primary endpoint will be complete response (CR) at 6 months from registration. This study will use the response criteria as described in section 11.0 to evaluate response or progression. The patients enrolled will have nonmeasurable disease on imaging and response will be evaluated with biopsy or cytology at 6 months post-registration. All patients meeting the eligibility criteria who have signed a consent form, have begun treatment, and have not been deemed a major treatment violation during the first cycle of treatment will be evaluable for response.

16.12 Safety run-in portion: The safety run-in portion will consist of the first 6 patients enrolled on the study. For a subject to be considered evaluable for dose-limiting toxicity (DLT) the subject must have received at least two doses of avelumab for cycles 1-2 and chemoradiation for cycle 3 (Day 29). If a subject withdraws from the study within the first 3 cycles of treatment for reasons other than adverse events, the subject will be replaced; and only DLTs occurring in Cycles 1-3 will be used for establishing safety during the run-in portion. However, all adverse event data will be summarized in the final analysis. These 6 patients will be included in the efficacy analysis. Safety for all patients (including the patients in the run-in portion) will continue to be monitored via the Adverse Event Stopping Rule. Dose limiting toxicity during cycle 3 (Day 29; in either portion) will be defined as described in section 7.0

16.2 Statistical Design

16.21 Decision Rule: The largest success proportion (CR at 6 months post-registration) where the proposed treatment regimen would be considered ineffective in this population is 65%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 85%. The following two-stage design based on properties of the binomial distribution uses 27 patients to test the null hypothesis that the true success proportion in a given patient population is at most 65%.

16.211 Stage I: Enter 12 patients into the study. If 8 or fewer successes are observed in the first 12 evaluable patients, the study will conclude or the investigators will discuss with the, IRB, or DSMB to determine if further investigation is warranted. Otherwise, if 9 or more successes are observed in the first 12 evaluable patients, we will proceed to Stage 2. Accrual will continue between Stage 1 and Stage 2 while patients become evaluable for the primary endpoint.

16.212 Stage 2: Enter an additional 15 patients into the study. If 20 or fewer successes are observed in the first 27 evaluable patients, we may consider this regimen ineffective in this patient population. If 21 or more successes are observed in the first 27 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.22 Sample Size: The two-stage study design to be utilized is fully described in Section 16.21. A minimum of 27 evaluable patients are to be accrued onto this study unless undue adverse events are encountered. We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Thus, **a maximum of 30 patients will be accrued onto this study** in order to have 27 evaluable patients available for the statistical design described in Section 16.21. There is no pre-specified maximum accrual for the two chemotherapy cohorts.

16.23 Accrual Time and Study Duration: The anticipated accrual rate is approximately 1-2 patients per month, based on physician estimate. Therefore, the accrual period for this phase II study

is expected to be 20 months. The final analysis can begin approximately 26 months after the trial begins, i.e., as soon as the last patient has completed the 6 months post-registration clinical follow-up visit.

16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is ≤0.10 and the probability of declaring that this regimen warrants further studies (i.e., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is…	0.65	0.70	0.75	0.80	0.85
Then the probability of stopping accrual after Stage I is …	0.65	0.51	0.35	0.21	0.09
And the probability of declaring that the regimen warrants further studies is …	0.10	0.22	0.42	0.65	0.85

16.25 Other Considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan: The analysis for this trial will commence at planned time points and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accordance with Mayo Clinic Cancer Center (MCCC) Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity.

16.31 Primary Endpoint

16.311 Definition: The primary endpoint of this trial is the proportion of patients who achieve a complete response (CR) at 6 months post-registration as defined in Section 16.11.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated using the properties of the binomial distribution.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.32 Definitions and Analyses of Secondary Endpoints

16.321 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.322 Analysis of Patient-Reported Outcomes (EORTC QLQ-30, EORTCQOL-BLM30) : Quality of life will be assessed at screening, at end of avelumab treatment, and EOS (12 month after registration). QOL will be measured using the EORTC QLQ-C30, a 30-item patient-reported questionnaire about patient ability to function, symptoms related to the cancer and its treatment, overall health and quality of life, and perceived financial impact of the cancer and its treatment. 28 of the 30 items are measured on a 1-4 scale (1=not at all; 4=very much) with the remaining two items (overall health and overall quality of life) scored on a 1-7 numeric analogue scale (1=very poor; 7=excellent). The recall period for the EORTC QLQ-C30 is one week. The EORTC QLQ-C30 is the product of more than a decade of collaborative research and to date, more than 2200 studies using the EORTC QLQ-C30 have been registered with the EORTC (Fayers et al, 2001 [EORTC Scoring Manual]). The EORTC QLQ-BLM30 is a 30-item questionnaire for patients with muscle invasive bladder cancer (T2, T3, T4a and T4b). The muscle-invasive bladder cancer module contains additional items assessing urostomy problems, problems associated with the use of a catheter, and body image.

A paper booklet containing all the patient-reported outcomes will be administered in clinic at baseline and every cycle visit at Mayo Clinic, and each PRO will be scored according to the published scoring algorithm. Scale score trajectories over time will be examined using stream plots and mean plots with standard deviation error bars overall. Changes from baseline will be statistically tested using paired t-tests, and standardized response means (mean of the change from baseline scores at a given cycle, divided by the standard deviation of the change scores) will be interpreted (after applying Middel's (2002) adjustment) using Cohen's (1988) cut-offs: <0.20 = trivial; 0.20-<0.50 = small; 0.50-<0.80 = moderate; and >=/0.80 = large. Correlation between outcomes will employ Pearson and/or Spearman correlations at individual time points.

16.323 Progression-Free Survival (PFS)**:** PFS will be defined as the time from registration to time of first documentation of progression (as defined in Section 11.b) or death due to any cause. Patients last known to be alive and not to have progressed are censored at the last day of contact (or at study completion – 12 months). PFS rate at 1 year will be estimated using the method of Kaplan-Meier (1958).

16.324 Recurrence-Free Survival (RFS): RSF will be defined as the time from documented complete response to the first documentation of recurrence (as defined in Section 11.c). Patients last known to be alive and not to have recurred are censored at the last day of contact (or at study completion – 12 months). RFS rate at 1 year will be estimated using the method of Kaplan-Meier (1958),

16.33 Exploratory & Correlative Endpoints: See section 2.3

16.34 Translational analyses: Given the small sample size, all translational analyses are considered exploratory and no adjustment for multiplicity will be employed. One-sided p-values ≤0.10 are considered statistically significant throughout. Results will be used to design subsequent confirmatory studies (likely as translational components within the subsequent phase III study should this phase II study support the use of this combination in a phase III study).

We will explore the relationship of PD-L1(SP263 and SP142),CD8+ by IHC and tumor mutational burden (Foundation Medicine Panel) and clinical response in order to identify if these markers may be predictive of response. Association of Bim Expression will be evaluated at using the baseline tissue specimen and explored in relation to 6 months post-registration response and subsequently in relation to other clinical outcomes such as tumor response and adverse event incidence using two-way tables and analyzed using Fisher's exact tests. Expression of immune signatures by RNA-sequencing (RNA-seq) expression (using the baseline tissue specimen) will be evaluated at baseline and explored in relation to clinical outcomes such as progression-free survival, tumor response, and adverse event incidence using two-way tables and box plots and analyzed using Fisher's exact tests or logistic regression methods, as appropriate.

16.4 Data & Safety Monitoring

16.41 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (ie, an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

• if 4 or more patients in the first 10 treated patients (or 40% after 20 patients have been accrued) experience a Grade 3 or higher non-hematologic adverse event.

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 26 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has completed the 6 months post-registration clinical follow-up.

16.6 Inclusion of Women and Minorities

16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of this treatment regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 Based on prior MCCC studies involving similar disease sites, we expect about 5% of patients will be classified as minorities by race and 25% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	2	3
Not Hispanic or Latino	6	21	27
Ethnic Category: Total of all subjects	7	23	**30**
American Indian or Alaskan Native	0	1	1
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
White	7	22	29
Racial Category: Total of all subjects	7	23	**30**

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Research Study (Section for more information)	Specimen Purpose (check all that apply)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	*Archived tissue*	Process at site? (Yes or No)	Tempera Conditi for Stor /Shippi
Correlative studies for mRNA expression and whole genome analysis *Correlative Application MC1752-C1*	☒ Correlative studies for mRNA expression and whole genome analysis	Optional	Formalin Fixed Paraffin Embedded	5 charged unstained slides 5 microns thick sections	*X*	*No*	Ambie

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Archived tissue may be collected per table 17.1 through next generation sequencing for mRNA expression and whole genome analysis

Block retrieval and cutting will be determined at a later date.

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue

17.321 Archived tissue may be collected per table 17.1 through next generation sequencing for mRNA expression and whole genome analysis

17.322 Block retrieval and cutting will be determined at a later date. Shipping, accessioning, and processing information will be determined at a later date. A modification will be submitted when information is available.

17.4 Background and Methodology

17.41 See section 1.5 for correlative background information.

17.42 Archived tissue may be collected per table 17.1 through next generation sequencing for mRNA expression and whole genome analysis.

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18.0 Records and Data Collection Procedures

18.1 Data submission instructions

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

Not applicable. Patients will be followed until EOS visit (12 months) only.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis prior to study entry as well as for evidence of response to study therapy and progression after study therapy.

18.6 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget Considerations

19.1 Tests to be research funded: Avelumab Study drug, Avelumab study drug administration, ECG, urogram at EOS visit (12 month after registration), obtaining and processing of archived research tissue specimens.

20.0 References

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐

Your birthdate (Day, Month, Year): ☐☐☐☐☐☐☐☐☐☐

Today's date (Day, Month, Year): 31 ☐☐☐☐☐☐☐☐☐☐

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix III EORTC QLQ-BLM30

EORTC QLQ - BLM30

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

PLEASE ANSWER QUESTIONS 31 - 37 ONLY IF YOU DO NOT HAVE A UROSTOMY

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had to urinate frequently **during the day**?	1	2	3	4
32.	Have you had to urinate frequently **at night**?	1	2	3	4
33.	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34.	Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35.	Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
36.	Have you had any unintentional release (leakage) of urine?	1	2	3	4
37.	Have you had pain or a burning feeling when urinating?	1	2	3	4

PLEASE ANSWER QUESTIONS 38 - 43 ONLY IF YOU HAVE A UROSTOMY

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
38.	Has urine leaked from your urostomy bag?	1	2	3	4
39.	Did you have problems with caring for your urostomy?	1	2	3	4
40.	Was your skin around the urostomy irritated?	1	2	3	4
41.	Have you felt embarrassed because of your urostomy?	1	2	3	4
42.	Have you been dependent on others for caring for your urostomy?	1	2	3	4
43.	Did you frequently have to change the urostomy bag?	1	2	3	4

PLEASE ANSWER QUESTION 44 ONLY IF YOU HAVE USED A CATHETER DURING THE PAST WEEK

44.	Have you had problems with self-catheterization? (inserting a tube in the bladder to pass urine)	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
45.	Were you worried about your health in the future?	1	2	3	4
46.	Did you worry about the results of examinations and tests?	1	2	3	4
47.	Did you worry about possible future treatments?	1	2	3	4
48.	Have you had a bloated feeling in your abdomen?	1	2	3	4
49.	Have you had flatulence or gas?	1	2	3	4
50.	Have you felt physically less attractive as a result of your illness or treatment?	1	2	3	4
51.	Have you been dissatisfied with your body?	1	2	3	4
52.	Have you felt less feminine/masculine as a result of your illness or treatment?	1	2	3	4

During the past 4 weeks:		Not at all	A little	Quite a bit	Very much
53.	To what extent were you interested in sex?	1	2	3	4
54.	To what extent were you sexually active (with or without sexual intercourse)?	1	2	3	4
55.	**For men only:** Did you have difficulty gaining or maintaining an erection?	1	2	3	4
56.	**For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?	1	2	3	4

Please answer the following 4 questions only if you have been sexually active during the past 4 weeks:		Not at all	A little	Quite a bit	Very much
57.	Have you felt uncomfortable about being sexually intimate?	1	2	3	4
58.	Have you worried that you may contaminate your partner during sexual contact with the bladder treatment you have been receiving?	1	2	3	4
59.	To what extent was sex enjoyable for you?	1	2	3	4

60.	**For Women only:** did you have a dry vagina or other problems during intercourse?	1	2	3	4

Appendix IV Patient Information Sheet

Patient Information Sheet
Screening & Active Monitoring Phase

You have been given a booklet to complete for this study. The booklet contains some questions about your health as a patient receiving treatment. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

This booklet contains:

- The EORTC QLQ-C30: complete during your scheduled clinic visit (Screening, end of avelumab treatment, end of study)
- The EORTC QLQ-BLM30: complete during your scheduled clinic visit (Screening, end of avelumab treatment, end of study)

Thank you for taking the time to help us.