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SWOG CANCER RESEARCH NETWORK

RANDOMIZED PHASE II TRIAL OF GEMCITABINE, AVELUMAB AND CARBOPLATIN VS. NO NEOADJUVANT THERAPY PRECEDING SURGERY FOR CISPLATIN-INELIGIBLE MUSCLE-INVASIVE UROTHELIAL CARCINOMA: SWOG GAP TRIAL

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by SWOG with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and NRG.

Additional site requirements include completion of a protocol specific Delegation of Task Log (DTL) (see Section 13.4e)

NCT# 04871529

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AGENTS:

Commercially Available Agents:

Gemcitabine (Gemzar®) (NSC-613327)
Carboplatin (CBDCA) (NSC-241240)

SWOG-Held IND Agents:

Avelumab (MSB0010718C; Bavencio®)
(NSC-799232) (IND-156359)

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Medical Queries (treatment or toxicity related questions):	Email: gurup_sonpavde@dfci.harvard.eduor call: Dr. Sonpavde at Phone: 617/632-2429
Investigational Drug questions:	See Protocol Section 3.0 orcontact the SWOG Operations Office at protocols@swog.org mailto:
Requests for Investigator's Brochures:	See Protocol Section 3.0 or contact the SWOG Operations Office at protocols@swog.org
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM)	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL)	See Protocol Section 14.1 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Section13.5 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Participant Transfers:	patienttransfer@crab.org
Serious Adverse Event Reporting questions:	See Protocol Section 8.6 Email: adr@swog.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION

For regulatory requirements:	**For participant enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with participants waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878)), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the participant enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires logging in with a CTEP-IAM username and password. or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users).

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS). Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.

For participant eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email:
206/652-2267
guquestion@crab.org

For treatment or toxicity related questions contact the Study Chairs by phone or email: Dr. Sonpavde or Dr. Liss by phone or email.

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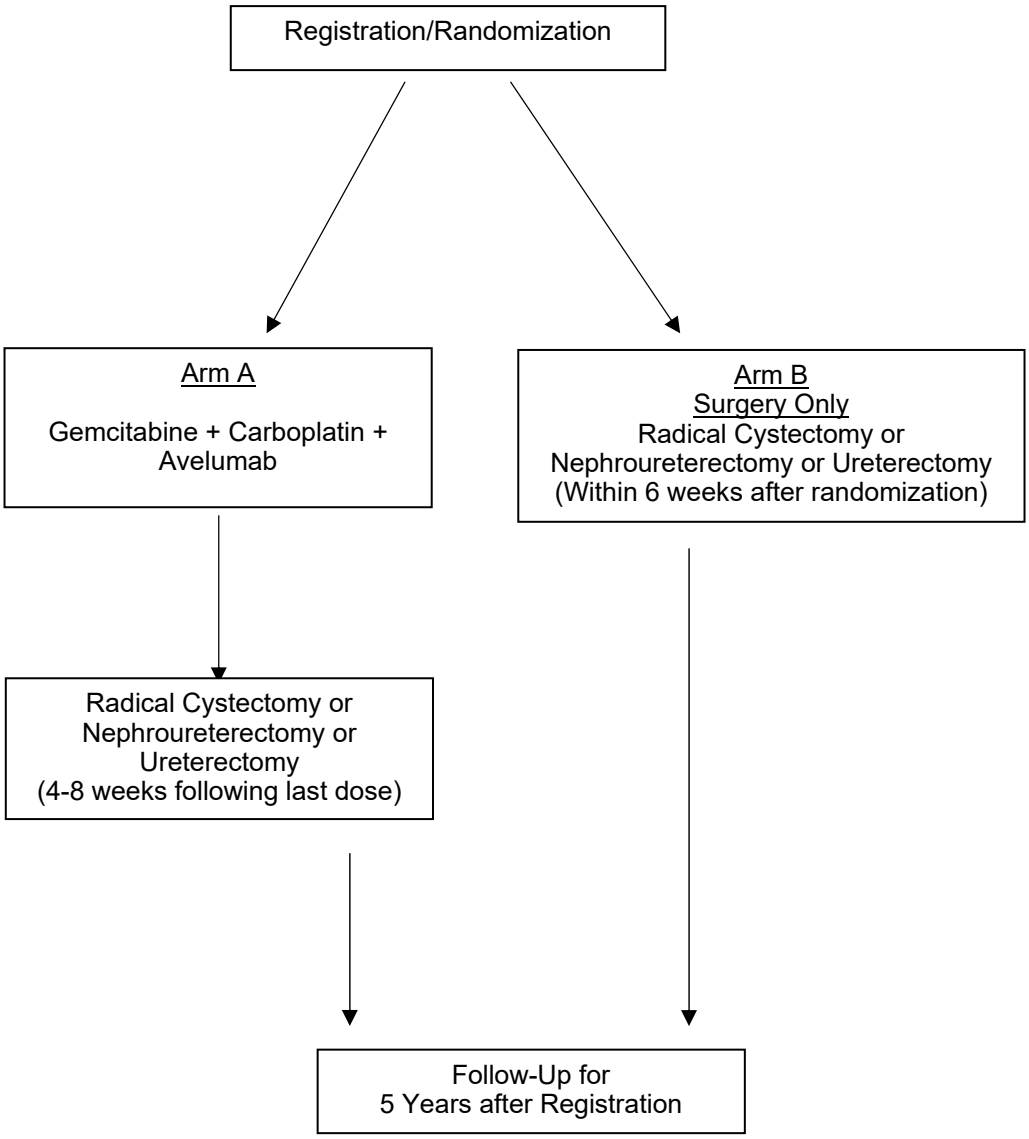
For non-clinical questions (i.e. unrelated to participant eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

SCHEMA


Registration/Randomization
Arm A
Gemcitabine + Carboplatin + Avelumab
Arm B
Surgery Only
Radical Cystectomy or Nephroureterectomy or Ureterectomy
(Within 6 weeks after randomization)
Radical Cystectomy or Nephroureterectomy or Ureterectomy
(4-8 weeks following last dose)
Follow-Up for
5 Years after Registration

1.0 OBJECTIVES

1.1 Primary Objective

a. To compare pathologic complete response (pCR, pT0N0) with avelumab plus gemcitabine and carboplatin (AGCa) vs. no neoadjuvant therapy preceding protocol surgery for muscle-invasive bladder cancer or upper tract urothelial carcinoma (MIBC/UTUC) for participants who are ineligible for cisplatin-based chemotherapy.

1.2 Secondary Objective(s)

a. To evaluate toxicities with AGCa, and to compare resectability rates and surgical complications by arm in this population.

b. To compare event-free survival (EFS) with AGCa versus no neoadjuvant therapy in this population.

c. To compare overall survival (OS) with AGCa versus no neoadjuvant therapy preceding surgery in this population.

d. To compare pathologic complete response (pCR, pT0N0) with avelumab plus gemcitabine and carboplatin (AGCa) vs. no neoadjuvant therapy preceding protocol surgery in the subset of participants who received at least 2 cycles of neoadjuvant therapy in Arm A.

1.3 Banking Objectives

a. To bank tumor tissue, blood, and urine for future correlative genomic, transcriptomic, and proteomic studies to discover molecular signatures associated with pCR and resistance.

2.0 BACKGROUND

2.1 Neoadjuvant Therapy for Bladder Cancer: Knowledge Gap and Unmet Clinical Need in the Setting of Cisplatin-Ineligible Patients

Level 1 data exist to support the use of neoadjuvant cisplatin-based combination chemotherapy preceding radical cystectomy (RC) for resectable (cT2-T4aN0M0) MIBC. *(1, 2, 3)* The **SWOG-8710** Phase III trial demonstrated significantly improved outcomes with neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy compared to no neoadjuvant chemotherapy with a 5-year overall survival (OS) of 57% vs. 43%. The Medical Research Council trial also demonstrated improved OS (49% vs. 43% at 5 years) as well as disease-free survival (39% vs. 32% at 5 years) with neoadjuvant CMV (cisplatin, methotrexate, vinblastine). *(2)* The depth of pathologic response has been shown to be associated with survival in the context of neoadjuvant cisplatin-based chemotherapy in the **SWOG-8710** trial, with the best outcomes seen with pCR (pT0), which was observed in ~38% of patients receiving MVAC chemotherapy compared to ~15% of patients in the RC alone arm. *(4)* However, data also suggest that the baseline age-dependent increase in renal dysfunction rendering patient's cisplatin-ineligible is common in MIBC and occurs in > 40% of patients > 70 year old. *(5)* Additionally, Zubrod-PS ≥ 2, neuropathy > Grade 1, hearing loss > Grade 1 and NYHA cardiac dysfunction > class 2 have been accepted as criteria determining that patients are cisplatin-ineligible. *(6)* For such patients who are cisplatin-ineligible or refuse cisplatin chemotherapy, there is no established data to support use of neoadjuvant (or adjuvant) therapy. Gemcitabine plus carboplatin (GCa) is considered a community standard for those with metastatic disease for patients that cannot receive cisplatin. *(7, 8, 9, 10, 11, 12, 13)* Small non-randomized

and retrospective studies report the feasibility and modest benefit from delivering neoadjuvant GCa; the pCR rates have been 16-24%, with a suggestion of improved PFS. *(14, 15, 16)* The uptake of neoadjuvant chemotherapy has been steadily increasing in the United States, and the application to cisplatin-ineligible patients will further increase its utility. *(17)* Nevertheless, there is no established neoadjuvant regimen for cisplatin-ineligible MIBC/UTUC. Thus, there is a significant knowledge gap and unmet need in the neoadjuvant therapy space for cisplatin-ineligible patients. One recently reported Phase III trial (POUT) evaluated adjuvant platinum-based chemotherapy (cisplatin or carboplatin) for UTUC and identified a disease-free survival benefit leading to early stopping of the trial. *(18)* Notably, in exploratory analyses, adjuvant GCa also appeared to be associated with benefit in the POUT trial, albeit to a lesser magnitude than gemcitabine plus cisplatin (GC), suggesting the hypothesis that GCa may confer benefits in the neoadjuvant setting for UTUC and MIBC also, albeit less than seen with GC. However, this trial only enrolled UTUC patients and did not evaluate neoadjuvant therapy, which appears more feasible to deliver.

2.2 Activity of Single Agent PD1/L1 Inhibitors in Urothelial Carcinoma

Atezolizumab, avelumab and durvalumab, programmed death (PD)-ligand (L)-1 inhibitors, and the PD-1 inhibitors nivolumab and pembrolizumab are approved for patients relapsing after platinum-based first-line therapy.*(19, 20, 21, 22, 23, 24)* All of these agents have similar activity with responses in ~20% of patients and manageable toxicities characterized by immune related adverse events. Atezolizumab and pembrolizumab are approved as first-line therapy for cisplatin-ineligible advanced UC with high PD-L1 expression or platinum-ineligible patients regardless of PD-L1 expression.*(25)* More recently, avelumab extended survival regardless of tumor PD-L1 status as switch maintenance therapy in those with responding or stable disease on platinum-based first-line chemotherapy.*(26)* Multiple PD1 and PD-L1 inhibitors are undergoing evaluation in Phase III trials as adjuvant therapy following RC for high risk disease with or without prior neoadjuvant chemotherapy. Unfortunately, the IMvigor010 Phase III trial did not report improved outcomes with adjuvant atezolizumab for unselected patients with MIBC, although the results of other trials evaluating pembrolizumab and nivolumab are still pending. *(27)*

Single agent pembrolizumab or atezolizumab appeared feasible with promising pathologic complete response rates (~30-40%) as neoadjuvant therapy followed by radical cystectomy for cisplatin-ineligible MIBC patients. *(28, 29, 30, 31)* Intriguingly, the pCR rate with pembrolizumab appeared to be associated with high tumor PD-L1 protein expression by IHC, tumor mutation burden (TMB) and gene expression profile. *(32, 33)* Multiparametric magnetic resonance imaging (MRI) appeared promising as a radiomic modality to predict pathologic response in this trial. *(34)* In the trial that evaluated neoadjuvant atezolizumab, preexisting activated T cells correlated with outcome. Responding tumors showed expression of genes related to tissue repair after treatment and stromal factors such as transforming growth factor (TGF)-β, fibroblast activation protein and cell cycle gene signatures were associated with resistance.

2.3 Activity of PD1/L1 Inhibitors in Combination with Platinum-Based Chemotherapy for Urothelial Carcinoma

PD-1 and PD-L1 inhibitors are being combined with platinum-based combination chemotherapy and cytotoxic T-lymphocyte associated (CTLA)-4 inhibiting immune modulators in first-line metastatic disease randomized Phase III trials, which allow cisplatin-ineligible patients regardless of PD-L1 expression.(24) Indeed, the IMvigor130 trial reported the improvement of progression-free survival with the combination of atezolizumab with platinum-based first-line chemotherapy for metastatic urothelial carcinoma regardless of tumor PD-L1 expression. *(35, 36)* In contrast, the Phase III DANUBE first-line trial did not meet the primary endpoints of improving OS compared to gemcitabine-platinum for a chemotherapy-free checkpoint inhibitor alone strategy of durvalumab in patients with high tumor/immune cell PD-L1 or for durvalumab plus tremelimumab regardless of PD-L1 expression. *(37)*

Recently reported Phase II trials evaluated neoadjuvant pembrolizumab or nivolumab in combination with cisplatin-based chemotherapy for cisplatin-eligible MIBC (NCT02736266, NCT023657)66). In the preliminary analysis, the authors note promising pathologic response activity for the combination of gemcitabine, cisplatin and pembrolizumab as neoadjuvant therapy for cisplatin-eligible patients with MIBC (the pCR rate was 44.4% and <pT2N0 rate was 61.1%). *(38)* In contrast to the single agent pembrolizumab data, pCR was observed regardless of tumor PD-L1 protein expression with combination gemcitabine-cisplatin-pembrolizumab Similar data were also reported in a phase II trial recently for the combination of gemcitabine, cisplatin and nivolumab. *(39)* Indeed, the combination of a PD1 inhibitor (pembrolizumab) with neoadjuvant chemotherapy significantly increased pCR rate in a phase III trial enrolling triple-negative breast cancer (which is biologically similar to urothelial carcinoma in many respects) regardless of tumor PD-L1 status. *(40)* Randomized phase III trials are planned to develop these chemo-immunotherapy combinations as neoadjuvant therapy for cisplatin-eligible MIBC patients (NCT03661320, NCT03732677, NCT03924856). Randomized phase III trials are also planned in the neoadjuvant cisplatin-ineligible space using an immunotherapy alone strategy without a chemotherapy backbone (NCT03924895, 2018-002676-40). However, none of the planned industry-sponsored trials are capitalizing on the potential additive or synergistic efficacy regardless of PD-L1 expression when combining PD1/PD-L1 inhibitors with chemotherapy for cisplatin-ineligible MIBC.

2.4 Rationale to Support the Development of Neoadjuvant Avelumab in Combination with Gemcitabine and Carboplatin for Cisplatin-Ineligible Muscle-Invasive Urothelial Carcinoma

A significant unmet need exists in the context of cisplatin-ineligible patients with MIBC/UTUC. Currently, MIBC or high risk UTUC patients who are cisplatin-ineligible are offered upfront RC, nephroureterectomy or ureterectomy followed by trials in the adjuvant setting. Single agent PD1/L1 inhibitors show promising activity in the neoadjuvant setting, which may be confined to selected patients with high PD-L1 or high TMB tumors. *(41, 42, 43, 44)* Indeed, the failure of adjuvant atezolizumab as adjuvant therapy for unselected MIBC patients in the IMvigor010 trial is also consistent with the hypothesis that benefit from single agent perioperative PD1/L1 inhibitors may be confined to a selected subset of patients. Inferior outcomes have also been observed for single agent pembrolizumab or atezolizumab compared to platinum-based chemotherapy as first-line therapy for low PD-L1 expressing metastatic urothelial carcinoma patients (https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm612484.htm), which led to a change in the regulatory indication sanctioning its use in those with high tumor PD-L1 expression. In contrast, there is a robust rationale to investigate PD1/PD-L1 inhibitors in combination with platinum-based chemotherapy as neoadjuvant therapy regardless of PD-L1 expression based on preliminarily promising data in the phase II neoadjuvant trials of cisplatin-eligible patients and the phase III IMvigor130 trial in the first-line metastatic disease setting. *(45, 46, 47, 48)* The tumor in place affords the possibility of capitalizing on a large antigenic burden and converting a large number of PD1 expressing exhausted T cells in the tumor stroma to competent T cells that may traffic systemically and eliminate microscopic metastatic disease. Furthermore, gemcitabine exhibits immune enhancing properties by clearing Tregs and MDSCs. *(49, 50)* The combination of PD1/L1 inhibitors with chemotherapy has also yielded benefits regardless of tumor PD-L1 expression in randomized trials of other malignancies with biologic similarities to urothelial carcinoma, e.g. triple negative breast cancer and small and non-small cell lung cancer. *(51, 52, 53, 54)* In contrast, single agent neoadjuvant PD1/L1 inhibitors may not yield robust benefits in unselected MIBC patients. Hence, given that GCa has yielded pathologic responses as neoadjuvant therapy and appears superior to PD1/L1 inhibitors in PD-L1 low patients as first-line therapy for metastatic urothelial carcinoma, it may represent a reasonable backbone to develop neoadjuvant therapy for cisplatin-ineligible MIBC in combination with a PD1/L1 inhibitor. Avelumab may also be expected to be feasible in combination with platinum-based chemotherapy, given similar efficacy and toxicity profiles for all PD1 and PD-L1 inhibitors; indeed, 1) the INDUCOMAIN phase II trial (NCT03390595) demonstrated

the safety and activity of the combination of gemcitabine, carboplatin and avelumab (n=42) as first-line therapy for patients with metastatic urothelial carcinoma who were ineligible for cisplatin-based chemotherapy and 2) a phase III trial (Javelin Ovarian-100) has evaluating and reported safety of avelumab combined with carboplatin-based combination chemotherapy for ovarian cancer. This design allows the optimization of neoadjuvant therapy using the combination of GCa and avelumab, which may confer benefits to a broad cisplatin-ineligible MIBC population regardless of PD-L1 expression, when compared to the current convention of no neoadjuvant therapy and upfront radical surgery.

This randomized phase II trial is comparing the current standard of upfront surgery without neoadjuvant therapy vs. the combination of carboplatin-based chemotherapy and PD-L1 inhibition as neoadjuvant therapy of cisplatin-ineligible muscle-invasive bladder cancer (MIBC) and high risk UTUC patients. This is the first randomized trial employing a strategy of combining cytotoxic chemotherapy and an immune checkpoint inhibitor for cisplatin-ineligible muscle-invasive bladder cancer and will provide transformative data in this space. Moreover, given that other industry-led randomized phase III trials evaluating checkpoint inhibitors in the neoadjuvant cisplatin-ineligible space are being planned without a chemotherapy backbone, this proposed trial will provide complementary evidence for a different strategy that leverages the known potentially additive or synergistic efficacy of GCa. This paradigm also offers the potential to interrogate tumor tissue and radiomics before and after therapy and identify a prognostic/predictive signature for benefit from the combination.(45, 46) While the level of pCR increment at the trial level that may translate to improved level long-term outcomes (PFS, OS) is unclear, a range of pCR improvement 1-19% was associated with improved long-term outcomes in the setting of breast cancer. Hence, a strong rationale may be made to apply these guidelines to MIBC and an increment in pCR rate from 15% to 35% (i.e. similar to the **SWOG8710** cisplatin-eligible trial) may be reasonably likely to translate to improved PFS and OS.(1-3) Notably, >80% of recurrence events occur within 2 years of RC, and a robust association of PFS at 2 years with OS at 5 years at the individual patient level has been established. *(55, 56, 57)* Correlative studies (tumor tissue genomics, transcriptomics and proteomics) may be utilized to develop precision medicine and understand tumor biology and resistance mechanisms. Noninvasive correlative studies including peripheral blood immune studies, circulating tumor (ct)-DNA profiling and radiomics alterations may complement efforts to develop precision medicine by correlating with pathologic outcomes. *(58, 59, 60, 61)*

2.5 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	2	7	0	0	9
White	26	147	2	7	182
More Than One Race	0	0	0	0	0

Total	29	158	2	7	196

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, gemcitabine and carboplatin are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, avelumab is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances, submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator's Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Avelumab (MSB0010718C; Bavencio®) (NSC-799232, IND-156359)

a. PHARMACOLOGY

Mechanism of Action: Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on antitumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

b. PHARMACOKINETICS

1. Absorption: Avelumab is administered intravenously and is 100% bioavailable.

2. Distribution: Avelumab is expected to be distributed in the systemic circulation and to a lesser extent into the extracellular space. In vitro studies suggest that avelumab binds to human tissues that are known for PD-L1 expression: various epithelial cell types, endothelium, mononuclear cells (including dendritic cells, lymphocytes, monocytes and macrophages), pancreatic islets, placental trophoblasts and decidual cells, smooth muscle cells, and mesenchymal stem cells. The volume of central and peripheral compartments are estimated to be 2.84L and 1.21L in the typical subject, respectively. The geometric mean Vss for a subject receiving 10mg/kg was 4.72L, which is consistent with distribution mainly limited to systemic circulation.

3. Metabolism: Avelumab is degraded by proteolytic catabolism. CYP450 does not contribute to its metabolism.

4. Elimination: The primary route of elimination of avelumab is through proteolytic degradation. The geometric mean clearance calculated by noncompartmental analyses [Study EMR100070-001] was estimated as 0.362mL/hr/kg for an initial 10mg/kg/dose. The corresponding value for Japanese subjects [Study EMR100070-002] was calculated as 0.471mL/hr/kg at the 10mg/kg dose. The estimate of clearance obtained for a typical subject in population pharmacokinetic analysis was 0.0246 L/hr. Population pharmacokinetic analysis and noncompartmental analysis results are comparable. Based on exposure efficacy and exposure safety relationships, there are no expected clinically meaningful

differences in the safety or efficacy of avelumab administered every 2 weeks at 800 mg or 10 mg/kg in patients with metastatic Merkel cell carcinoma, urothelial carcinoma, and advanced renal cell carcinoma.

c. ADVERSE EFFECTS

1. Adverse Effects:

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1738 patients.* Below is the CAEPR for Avelumab.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.0, April 23, 2019[1]

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
		Adrenal insufficiency[2]
		Hyperthyroidism[2]
		Hypophysitis[2]
		Hypopituitarism[2]
	Hypothyroidism[2]	
EYE DISORDERS		
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Diarrhea	
	Nausea	
	Pancreatitis[2]	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Chills	
Fatigue		
	Fever	
	Flu like symptoms[3]	
HEPATOBILIARY DISORDERS		
		Hepatic failure[2]
		Hepatobiliary disorders - Other (autoimmune hepatitis, immune-related hepatitis)[2]
IMMUNE SYSTEM DISORDERS		
		Autoimmune disorder[2]
		Cytokine release syndrome[3]
		Immune system disorders - Other (sarcoidosis)[2]
INFECTION AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction[3]	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	CPK increased	
	Creatinine increased	
	GGT increased	
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
	Thyroid stimulating hormone increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Hyperglycemia[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n= 1738]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Generalized muscle weakness	
	Muscle cramp	
	Myalgia[2]	
		Myositis[2]
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
		Encephalopathy[2]
		Guillian-Barre syndrome[2]
		Myasthenia gravis[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]
		Peripheral motor neuropathy
		Peripheral sensory neuropathy[2]
RENAL AND URINARY DISORDERS		
		Renal and urinary disorders - Other (immune related nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
		Pneumonitis[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Eczema	
	Pruritus	
	Rash acneiform	
	Rash maculo-papular	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Immune-mediated adverse reactions have been reported in patients receiving avelumab. Adverse events potentially related to avelumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of avelumab), administration of corticosteroids and supportive care.

[3] Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of avelumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of avelumab.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on avelumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that avelumab caused the adverse event:

CARDIAC DISORDERS - Palpitations; Sinus tachycardia
EYE DISORDERS - Blurred vision; Dry eye
GASTROINTESTINAL DISORDERS - Abdominal distension; Constipation; Dry mouth; Dyspepsia; Flatulence; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Electrocardiogram QT corrected interval prolonged; Investigations - Other (c-reactive protein increased); Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare); Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysgeusia; Headache; Tremor
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension

Note: Avelumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Based on its mechanism of action, avelumab can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with avelumab and for at least one month after the last dose of avelumab. There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise lactating women not to breastfeed during treatment and for at least one month after the last dose of avelumab due to the potential for serious adverse reactions in breastfed infants.

3. Special Populations: No dedicated clinical studies have been conducted to evaluate the effect of renal or hepatic impairment on the pharmacokinetics of avelumab. Even though a limited number of patients with severe renal impairment have been studied renal impairment is not expected to have an effect on the pharmacokinetics of avelumab. There are limited data from patients with severe hepatic impairment, and the effect of severe hepatic impairment on the pharmacokinetics of avelumab is not known.

4. Drug Interactions: No interaction studies have been conducted with avelumab in humans.

Note: Avelumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Avelumab is supplied by Merck KGaA/EMD Serono, Inc. and distributed by McKesson as single-use 200 mg vials containing a sterile solution of 10 mL total volume (20 mg/ml). Avelumab is a clear and colorless to slightly yellow concentrate for solution containing D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, and water for injection, and supplied in glass vials closed with a rubber (not made with natural rubber latex) stopper and sealed with an aluminum crimp seal closure fitted with a removable plastic cap.

f. STORAGE, PREPARATION & STABILITY

1. Avelumab must be stored under refrigeration (2°-8° C, 36-46º F) and protected from light until use. Avelumab must not be frozen. Rough shaking must be avoided during handling and preparation.

2. Avelumab must be diluted in 0.9% sodium chloride solution. Avelumab may also be diluted in 0.45% sodium chloride solution, if necessary. Prepared solutions of avelumab should be used immediately. If not used immediately, diluted avelumab may be stored for up to 4 hours at room temperature (15°C-25°C) or up to 24 hours under refrigeration (2°C to 8°C); this includes infusion time.

g. DRUG ORDERING AND ACCOUNTABILITY

1. Drug ordering: Drug orders must be submitted by faxing the Drug Order Form – SWOG S2011 to McKesson at the number listed on the order form. This form can be found on the SWOG website (www.swog.org) or on the CTSU website (www.ctsu.org).

2. Drug Handling and Accountability: Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug Returns: Unused or expired drug supplies MUST be returned to McKesson for disposal. Any partially opened vials need to be destroyed on site per institutional policy.

4. Questions about drug orders, transfers, returns, or accountability should be addressed to protocols@swog.org.

3.2 Gemcitabine hydrochloride (Gemzar®) (NSC-613327)

a. PHARMACOLOGY

Mechanism of Action:
Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

b. PHARMACOKINETICS

1. Absorption and Distribution: Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible. The volume of distribution is increased with the infusion duration. In a pharmacokinetics study of patients with various solid tumors, the volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions (70 to 285 minutes), the volume of distribution rose to 370 L/ m^2.

2. Metabolism: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. The gemcitabine di- and tri-phosphates do not appear to circulate in plasma in measurable amounts. Gemcitabine is metabolized by the liver to form the inactive uracil derivative, 2'-deoxy-2',2'-difluorouridine (dFdU). The inactive metabolite does not appear to accumulate with weekly dosing; however, it is excreted by the kidneys and may accumulate in patients with decreased renal function.

3. Elimination: Following a single 1,000 mg/m^2/30 min [^{14}C]-gemcitabine infusion, 92% to 98% of the dose was recovered within 1 week after gemcitabine administration. Urinary excretion of the parent drug and the dFdU metabolite accounted for 99% of the excreted dose, and less than 1% of the dose was excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

   Clearance of gemcitabine is affected by age and gender and is lower in women and the elderly. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Studies showed that gemcitabine half-life for short infusions ranged from 42 to 94 minutes, for long infusions it varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The terminal phase half-life for the active metabolite, gemcitabine triphosphate, in mononuclear cells ranges from 1.7-19.4 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of gemcitabine:
Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in >20% to 100% of subjects treated with gemcitabine include: flu-like symptoms, nausea, vomiting, rash, alopecia, infection, myelosuppression including anemia, leukopenia, neutropenia, and thrombocytopenia, muscle weakness, hematuria, paresthesia, sensory neuropathy, fatigue, somnolence, peripheral edema.

Adverse effects reported in 4% to 20% of subjects include: diarrhea, constipation, stomatitis, dyspnea, capillary leak syndrome, posterior reversible encephalopathy syndrome (PRES), extravasation.

Adverse effects reported in 3% or less of subjects include: arrhythmias, supraventricular arrhythmias, congestive heart failure, myocardial infarction, desquamation and bullous skin eruptions, gangrene, cerebrovascular accident, hepatic failure, adult respiratory distress syndrome (ARDS), anaphylaxis, renal failure, pulmonary fibrosis, pulmonary edema, and Interstitial pneumonitis, hemorrhage, hypertension, sepsis.

2. Pregnancy and Lactation: Category D. Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of < 2 mg/m^2. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.

3. Drug Interactions: Per gemcitabine package insert, no formal drug interaction studies have been performed to date. When gemcitabine was administered with carboplatin or paclitaxel there was minimal or no effect on the pharmacokinetics of the studied drugs.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Gemcitabine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.3 Carboplatin (CBDCA) (NSC-241240)

a. PHARMACOLOGY

Mechanism of Action: Carboplatin (CBDCA) is a hydrophilic platinum coordination compound and is an analog of cisplatin, producing intrastrand DNA cross-links.

b. PHARMACOKINETICS

1. Distribution: Vd = 16 L

2. Protein Binding: Carboplatin is not bound to plasma proteins.

3. Elimination: The initial half-life is 1.1 - 2.0 hours and the post-distributional half-life is 2.6 - 5.9 hours. Sixty-five percent of the dose is excreted in the urine within twelve hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of Carboplatin:
Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

2. Pregnancy and Lactation: Pregnancy Category D. Carboplatin may cause fetal harm, therefore women of childbearing potential should be advised to avoid becoming pregnant.

3. Drug Interactions: Due to potential drug interactions, a complete patient medication list, including Carboplatin, should be screened prior to initiation of and during treatment with Carboplatin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Carboplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

4.0 STAGING CRITERIA

4.1 Staging Criteria (AJCC, Eighth Edition)

Bladder

T2	Tumor invades the muscularis propria
T3	For renal pelvis only: Tumor invades beyond muscularis into peripelvic fat or into the renal parenchyma For ureter only: Tumor invades beyond muscularis into periureteric fat
T4a	Extravesical tumor directly invades any of the following: Prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall or abdominal wall

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

M0 No distant metastasis

Upper tract
T2 Tumor invades the muscularis
T3 For renal pelvis only: Tumor invades beyond muscularis into peripelvic fat or into the renal parenchyma. For ureter only: Tumor invades beyond muscularis into periureteric fat
T4 Tumor invades adjacent organs, or through the kidney into the perinephric fat

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis

M0 No distant metastasis

4.2 Method of staging

Contrast-enhanced computed tomography of the chest, abdomen, and pelvis should be performed for tumor stage assessments whenever possible. Images should be acquired with slice thickness of 5 mm or less. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

If a participant has a contraindication for CT IV contrast, a non-contrast CT of the chest and a gadolinium contrast-enhanced MRI of the abdomen and pelvis may be obtained.

If a contraindication for both MRI and CT intravenous contrasts exists, a non-contrast CT of the chest and a non-contrast MRI of the abdomen and pelvis should be obtained.

If a participant has contraindication for MRI (e.g., pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen and pelvis is acceptable.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a participant to be considered eligible for registration in OPEN. Section 5 may be printed and used to by the site, but is not to be uploaded in RAVE (unless specially stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.3). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or guquestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).**

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient participant scheduling without exceeding the guidelines.

5.1 Disease Related Criteria

a. Participants must have one of the following:

- A histologically documented muscle-invasive bladder carcinoma (MIBC) from TURBT within 120 days prior to registration.

- All participants must have a TURBT (or re-TURBT) within 70 days prior to registration and are eligible even if there is no muscle-invasion present in the re-TURBT.

- A histologically confirmed high grade upper tract urothelial carcinoma (UTUC) within 120 days prior to registration, with invasion confirmed by either a mass on cross-sectional imaging or a tumor directly visualized during upper urinary tract endoscopy within 120 days prior to registration.
  - All participants require a ureteroscopy with biopsy if feasible (or re-biopsy) within 70 days prior to registration and are eligible even if there is no muscle-invasion present in the re-biopsy.

Participants diagnosed with mixed urothelial carcinoma and variant histology within 120 days prior to registration may be eligible if the majority (>50%) of the tumor consists of urothelial carcinoma. Participants with pure non-urothelial variant histologies or any small cell histology are not eligible.

b. Participants must have clinical stage T2-T4aN0M0 bladder or upper tract cancer confirmed by radiologic staging (CT scan/MRI abdomen and pelvis, and CT scan/x-ray of the chest) within 56 days prior to registration.

c. Participants must have a bone scan within 56 days prior to registration if they have bone pain or elevated serum alkaline phosphatase.

5.2 Prior/Concurrent Therapy Criteria

a. Participants must not have received prior systemic chemotherapy, immunotherapy or radiotherapy for the treatment of muscle invasive bladder cancer (MIBC) or upper tract urothelial carcinoma (UTUC). Other prior pelvic radiotherapy is allowed if it does not preclude surgery (radical cystectomy, nephroureterectomy or ureterectomy, based on location of primary tumor). Prior intravesical therapy is allowed.

b. Participants must not have received immunosuppressive medication within 14 days prior to registration, with the exception of intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection) systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.

5.3 Clinical/Laboratory Criteria

a. Participants must be ≥ 18 years of age.

b. Participants must have Zubrod Performance Status 0-2 (see Section 10.4).

c. Participants must have history and physical examination within 28 days prior to registration.

d. Participants must be surgical candidates as deemed by the local site oncologic surgeon within 28 days prior to registration. This must be clearly documented.

e. Participants must have a serum creatinine ≤ the IULN OR measured OR calculated creatinine clearance ≥ 30 mL/min using the Cockroft-Gault Formula below. This specimen must have been drawn and processed within 28 days prior to registration:

Calculated Creatinine Clearance = $\frac{(140 - \text{age}) \times (\text{weight in kg})^{\dagger}}{72 \times \text{serum creatinine}^{*}}$

Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

f. Participants must be deemed cisplatin-ineligible based on greater than or equal to 1 of the following:
- Zubrod performance status=2
- creatinine clearance (calculated by Cockroft-Gault formula or measured) 30 to <60 ml/min,
- neuropathy >grade 1
- hearing loss >grade 1
- congestive heart failure >grade 2.

g. Participants must have adequate organ and marrow function as defined below within 28 days prior to registration:

– hemoglobin	≥ 9.0 g/dL
– absolute neutrophil count	≥ 1,500/mcL
– platelets	≥ 100,000/mcL
– total bilirubin	≤ 1.5 x institutional upper limit of normal (ULN) , (≤ 3 x ULN if Gilbert's disease)
– AST	≤ 2.5 × institutional ULN
– ALT	≤ 2.5 × institutional ULN

h. Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (see Appendix 18.1) and be class 2B or better.

i. Participant must not have any other prior malignancy except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, prostate cancer Gleason score ≤ 3+4 in active surveillance, adequately treated Stage I or II cancer from which the participant is currently in complete remission, or any other cancer from which the participant has been disease free for two years.

j. Participants must not be pregnant or nursing due to the risk of harm to a fetus or nursing infant. Women/men of reproductive potential must have a negative serum or urine pregnancy test within 28 days prior to registration and must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate participant chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

k. Participants with known human immunodeficiency virus (HIV) must be on effective anti-retroviral therapy and have undetectable viral load at their most recent viral load test and within 6 months prior to registration.

l. Participants must not have a history of active primary immunodeficiency.

m. Participants must not have a history of or active autoimmune or inflammatory disorder, with the exception of vitiligo, alopecia, hypothyroidism (stable on hormone replacement), or chronic skin condition that does not require systemic therapy.

5.4 Specimen Submission Criteria

a. Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.1.

5.5 Regulatory Criteria

a. Participants ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

NOTE: As a part of the OPEN registration process (see Section 13.2 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Participants will be randomized 1:1 using a dynamic balancing algorithm with stratification based on the following factors:

a. Clinical stage (cT2N0M0 vs cT3-4aN0M0)

b. Zubrod performance status (0-1 vs 2)

c. Calculated or measured creatinine clearance 30 to < 60 vs ≥ 60 ml/min

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Sonpavde at 617/632-2429. For surgery related questions, please contact Dr. Liss at 210/567-1100. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Participants on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

It is recommended that participants have a bimanual examination under anesthesia within 120 days prior to registration for both Arms A and B.

7.1 Treatment

a. Arm A: Gemcitabine + Carboplatin + Avelumab + Surgery

Initiation of treatment for Arm A must be planned to start no more than 14 calendar days after registration. Surgery must be planned within 4-8 weeks of last dose of neoadjuvant treatment.

Agent	Dose	Route	Day	Schedule*
Gemcitabine	1000 mg/m^2	IV over 30m	1, 8	Every 3 weeks x 4
Carboplatin	AUC 4.5**	IV over 30m	1	Every 3 weeks x 4
Avelumab	800 mg	IV over 60m	1	Every 2 weeks x 6

* 1 Cycle = 21 days. See Table 7.1a below for an outline of how study treatment falls across days within each cycle and within the overall weeks of study treatment. See also section 9.1.
** Note: Escalate to AUC 5 from Cycle 2 forward if no dose limiting toxicities

Table 7.1a: Study Treatment Timing

	Cycle 1			Cycle 2			Cycle 3			Cycle 4		
Day of Cycle	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15
Gemcitabine	X	X		X	X		X	X		X	X	
Carboplatin	X			X			X			X		
Avelumab	X		X		X		X		X		X	
Week of Overall Treatment	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12

Gemcitabine should be given first, then carboplatin, then avelumab (to be given in order listed in table above).

Avelumab is given after pre-medications acetaminophen 650 mg PO plus diphenhydramine 25-50 mg IV/PO. Monitor participants for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue avelumab for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions.

If avelumab has to be held for toxicities, gemcitabine and carboplatin may continue with dose modifications if necessary, for gemcitabine/carboplatin related toxicities. If gemcitabine and/or carboplatin are held for toxicities related to gemcitabine/carboplatin, avelumab may continue if no prohibitive toxicities related to avelumab are observed.

SURGERY

Radical Cystectomy, Nephroureterectomy or Ureterectomy

Radical cystectomy will be scheduled per surgeon's discretion as standard of care procedure, within 4-8 weeks after final neoadjuvant therapy in Arm A. Surgical approach (open, laparoscopic, or robotic assistance) is at surgeon's discretion. At minimum, a standard lymph node dissection must be performed at the time of the radical cystectomy. All potential node bearing tissue should be removed within the following boundaries: laterally the genitofemoral nerve; distally Cooper's ligament to include the lymph node of Cloquet; proximally the common iliac bifurcation; medially the bladder to include the tissue medial to the hypogastric artery; and posteriorly the floor of the obturator fossa with circumferential mobilization of the external iliac artery and vein unless contraindicated due to extensive atherosclerotic vascular disease.

In participants proceeding to nephroureterectomy or ureterectomy for upper tract urothelial carcinoma, regional template lymph node dissection is performed per

surgeon discretion within 4-8 weeks after final neoadjuvant therapy. Urinary bladder cuff is routinely excised, and regional lymph node dissection is performed according to tumor location, including hilar, paracaval, retrocaval, and inter-aortocaval nodes for right renal pelvic, proximal, and/or mid ureteral tumors; hilar and para-aortic nodes for left renal pelvic, proximal, and/or mid ureteral tumors; and ipsilateral common iliac, external iliac, internal iliac, and obturator nodes for distal ureteral tumors. Given little prospective data on the utility of routine lymph node dissection in UTUC, template-based lymphadenectomy is encouraged, but is not mandated.

b. Arm B: Surgery Only

Surgery should be performed within 6 weeks after registration.

Surgery (Radical Cystectomy, Nephroureterectomy or Ureterectomy)

Radical cystectomy will be scheduled per surgeon's discretion as standard of care procedure, within 6 weeks from registration in Arm B. Surgical approach (open, laparoscopic, or robotic assistance) is at surgeon's discretion. At minimum, a standard lymph node dissection must be performed at the time of the radical cystectomy. All potential node bearing tissue should be removed within the following boundaries: laterally the genitofemoral nerve; distally Cooper's ligament to include the lymph node of Cloquet; proximally the common iliac bifurcation; medially the bladder to include the tissue medial to the hypogastric artery; and posteriorly the floor of the obturator fossa with circumferential mobilization of the external iliac artery and vein unless contraindicated due to extensive atherosclerotic vascular disease.

In participants proceeding to nephroureterectomy or ureterectomy for upper tract urothelial carcinoma, regional template lymph node dissection is performed per surgeon discretion, within 6 weeks after registration. Urinary bladder cuff is routinely excised, and regional lymph node dissection is performed according to tumor location, including hilar, paracaval, retrocaval, and inter-aortocaval nodes for right renal pelvic, proximal, and/or mid ureteral tumors; hilar and para-aortic nodes for left renal pelvic, proximal, and/or mid ureteral tumors; and ipsilateral common iliac, external iliac, internal iliac, and obturator nodes for distal ureteral tumors. Given little prospective data on the utility of routine lymph node dissection in UTUC, template-based lymphadenectomy is encouraged, but is not mandated.

7.2 Disease/Recurrence Assessment

Participants' disease will be followed for 5 years after registration.

See Section 9.0 for disease assessment time points

ARM A: Disease assessment at the end of neoadjuvant systemic therapy, but prior to surgery (CT/MRI abdomen and pelvis, and x-ray/CT of the chest).

ARMS A and B: CT/MRI abdomen and pelvis, and x-ray/CT of the chest approximately every 12 weeks following surgery for 2 years, followed by CT/MRI abdomen and pelvis, and x-ray/CT chest annually in years 3-5. Disease assessment timing is to be based on calendar timing counted as weeks after registration, not based on cycles or drug administration.

7.3 DMU Demography monitoring and enrolling patients via OPEN

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

7.4 Criteria for Removal from Protocol Treatment

a. Neoadjuvant Therapy

1. Progression/recurrence of disease or symptomatic deterioration per participant or physician judgment (as defined in Section 10.1).

2. Unacceptable toxicity.

3. Systemic treatment delay for any reason > 21 calendar days.

4. The participants may withdraw from the protocol treatment at any time for any reason.

5. Starting non-protocol anti-cancer therapy.

b. Surgery

1. Refusal of surgery.

2. Delay of surgery greater than 8 weeks after last neoadjuvant treatment (Arm A) or greater than 6 weeks after registration (Arm B).

7.5 Discontinuation of Treatment

All reasons for discontinuation of systemic treatment must be documented in the Off Systemic Treatment Notice.

7.6 Follow-Up Period

All participants will be followed until death or 5 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Considerations

a. No dose reductions are allowed for avelumab. Dose delays are allowed as outlined below.

b. The maximum systemic treatment dose delay for any reason is 21 days.

c. Missed doses will not be made up.

d. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

e. Reductions are based on the dose being given at the end of the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

f. If a drug must be permanently discontinued, the participant must be removed from protocol therapy.

In order to provide optimal patient care, investigator discretion and institutional policies may be used in the prescribing of all supportive care drug therapy including, but not limited to antimicrobials, anti-emetics, G-CSF, PRBC, or platelet transfusion, etc. Pre-medications used for standard treatments for carboplatin, gemcitabine, and if needed, for avelumab as per the package insert.

The following criteria must be met within 3 days prior to starting day 1 of any cycle:

- ANC ≥ 1500 cells/mm^3
- Hemoglobin > 9 g/dl
- Platelet ≥ 100,000/mm^3
- Bilirubin ≤ 1.5 x ULN (≤ 3 x ULN if Gilbert's disease)
- Creatinine clearance ≥ 30 ml/min

For Cycle 2 and beyond, Day 1 and Day 8 treatment may be given using a +/- 3-day window. A treatment cycle may be delayed up to 5 days for inclement weather, major holiday, serious illness of a family member, or vacation that cannot be rescheduled without being a protocol deviation.

If there is a treatment delay of > 21 days, participants will be removed from systemic protocol treatment.

Supportive Care

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. During the study, supportive therapy can include antibiotics, analgesics, pain control, transfusions, psychotherapy, growth factors, hydration or any other symptomatic therapy as clinically indicated. Steroids will be allowed to treat any immune-related adverse events from avelumab as outlined in Section 8.3 for management of immune-related adverse events.

Treatment modification for symptoms of infusion-related reactions will be per institutional guidelines. For severe/life threatening (Grade 3 or 4) avelumab related infusion reactions, discontinue avelumab and manage anaphylaxis per institutional guidelines.

8.3 Dose Modifications and Delays

Carboplatin and gemcitabine

Note: Dose modification guidelines are recommendations not requirements. Sites may use institutional guidelines if preferred.

Up to 2 dose reductions are allowed for carboplatin and gemcitabine. Once dose is reduced, no subsequent escalations are recommended. If avelumab has to be held for toxicities, gemcitabine and carboplatin may continue with dose modifications if necessary, for gemcitabine/carboplatin related toxicities.

Cycle 2 Day 1: The dose modification guidelines for gemcitabine and carboplatin for hematologic toxicity on Day 1 of Cycle 2 and subsequent cycles is mentioned below.

ANC		**Platelet count**	**Gemcitabine**	**Carboplatin**
≥1500/mm^3	And	≥100,000/mm^3	Give 100% dose	Give 100% dose
< 1500/mm^3	and/or	<100,000/mm^3	Delay treatment by 1 week; Reduce dose for subsequent cycles by 25%	Delay treatment by 1 week; Reduce dose for subsequent cycles by AUC=1

The dose modification guidelines for gemcitabine and carboplatin for hematologic toxicity on Day 8 of Cycle 1 and subsequent cycles is mentioned below.

ANC		**Platelet count**	**Gemcitabine**
≥1,000/mm^3	and	≥ 75,000/mm^3	Give 100% dose
≥1,000/mm^3	and	50,000-74,999	Give 75% dose
<1,000/mm^3	or	< 50,000/mm^3	Skip treatment. Reduce dose by 25% for next treatment.

Primary prophylaxis with G-CSF should be considered with subsequent cycles if participants develop neutropenic complications in the immediate previous cycle. If febrile neutropenia requiring antibiotic therapy or Grade 4 thrombocytopenia occurs, the gemcitabine dose will be reduced by 25% for subsequent treatment cycles. The dose of

carboplatin may be reduced by AUC=1 for subsequent treatment cycles at the discretion of treating physician.

If a Day 8 gemcitabine is withheld due to hematologic toxicity, it will be skipped and not be given at a later date and the cycle will continue with Day 1 of the next cycle of treatment.

Avelumab

No dose modifications are permitted for avelumab.

If gemcitabine and/or carboplatin are held for toxicities related to gemcitabine/carboplatin, avelumab may continue if no prohibitive toxicities related to avelumab are observed. Avelumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities.

Infusion-related reactions include pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. The rate of infusion is interrupted or slowed for mild or moderate Grade 1-2 infusion-related reactions, with consideration of resuming the usual infusion-rate when symptoms revert to grade 1 or less. The infusion is stopped and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions

Avelumab may be suspended for most Grade 2 toxicities including immune related adverse events. Grade 3 toxicities including immune related adverse events generally warrant suspension of avelumab. Permanent discontinuation of avelumab is recommended with Grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to grade adverse events. A copy of the CTCAE Version 5.0 can be downloaded: (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf). Management of toxicities from gemcitabine and carboplatin will be per the package insert and standard institutional guidelines. The management of avelumab related immune adverse events are per physician discretion. Corticosteroids may be administered for Grade 2 toxicities. Grade ≥3 immune adverse events require the initiation of high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.

8.4 White blood Cell Growth Factors

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines (http://jco.ascopubs.org/content/24/19/3187.full) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Sonpavde at 617/632-2164 or Michael Liss at 210/567-1100.

8.6 Adverse Event/Serious Adverse Event Reporting Guidance

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rule's evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

If you have questions about this process, please contact the SAE Program Manager 210-614-8808 or email adr@swog.org.

8.7 Adverse Events Related to COVID-19

Infections occurring in participants on clinical trials are considered adverse events and should be reported per protocol guidelines via normal procedures (on CRFs/Rave and via CTEP-AERS if serious).

Please document COVID-19 related adverse events as follows:

Infections and infestations - Other, specify
Specify = COVID-19

Additionally, please record (and if applicable, report via CTEP-AERS) any other Adverse Events the subject experiences such as Dyspnea, Acute respiratory distress syndrome, etc.

CTEP-AERS specific instructions:

- **Narrative:** Identify all pertinent facts related to the COVID-19 infection including, but not limited to the following:
  - Presumptive vs confirmed diagnosis. If presumptive, please update your narrative if/when diagnosis is confirmed, including timelines.
  - Treatment information
  - Recovery information, including timelines
  - Outcome information/status
- **Supporting documentation:** Please fax supporting documentation including admission notes, progress notes, clinical visits, and discharge summary if/when available.
  - Fax Number: 301-897-7404, include protocol number, ticket number and subject ID on the fax cover sheet and each page faxed.

Queries:
CTEP-AERS Questions/Help:
Email: ctephelpdesk@nih.gov
Phone: 1-888-283-7457

8.8 Serious Adverse Event Reporting Requirements

a. Definition and Purpose

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (FDA, 21 CFR 312.32). See Table 8.1 for definition of a Serious Adverse Event (SAE) and reporting requirements.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of participant safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 8.1) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org . An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report via CTEP-AERS within the number of calendar days of learning of the event specified in Table 8.1.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the participant must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the participant has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 8.1. The investigational agent used in Arm A of this study is avelumab. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted on-line please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.1.

Table 8.1

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] [Avelumab] ([Arm A]).

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **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 participant 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 NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 8.6f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 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 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 1-2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission – Within **5 calendar days** submit documentation supporting the CTEP-AERS report to the SWOG Operations Office by fax 210-614-0006. Specific instructions will be sent by email to the reporting site by the SAE Program Manager.

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. 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.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic 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.

   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.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. Supporting documentation must also be submitted to SWOG Operations Office by fax to 210-614-0006.

   NOTE: If a participant has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for participants on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy Loss is defined in CTCAE as "Death in utero." Pregnancy Loss should be reported expeditiously as **Grade 4**

"Pregnancy Loss" under the Pregnancy, puerperium and perinatal conditions SOC.

A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a participant death.

3. **Death Neonatal** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth". A neonatal death should be reported expeditiously as **Grade 4 "Death Neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a participant death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 210-614-0006. 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 of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

9.0 STUDY CALENDAR

9.1 Arm A: Gemcitabine + Carboplatin + Avelumab + Surgery

	PRE-REG	Cycle 1			Cycle 2			Cycle 3			Cycle 4			At end of systemic therapy	4-8 weeks post systemic therapy	90 days post surgery	At progression /recurrence	Follow up after progression /recurrence
		W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12					
		(Each cycle = 21 days)																
PHYSICAL																		
History & Physical Exam	X	X	X	X	X	X		X	X	X	X	X			X			
Weight & Zubrod Performance Status	X	X	X	X	X	X		X	X	X	X	X			X			
Disease Assessment (A)	X													X		Every 12 weeks following surgery for years 1-2, every 6 months for year 3, then annually in years 4-5		Annually
Toxicity Notation	X	X[G]	X[G]	X[G]	X	X		X	X	X	X	X		X	X	X		
LABORATORY																		
Pregnancy test (urine or blood) in women of child-bearing potential	X																	
Complete Metabolic Panel [B]	X	X	X	X	X	X		X	X	X	X	X		X	X	X		
Complete blood cell counts (Hb, hematocrit, WBC, ANC (absolute neutrophil count), platelet	X	X	X		X	X		X	X		X	X		X		X		
TSH, free T4	X							X								X		

	PRE-REG	Cycle 1			Cycle 2			Cycle 3			Cycle 4			At end of systemic therapy	4-8 weeks post systemic therapy	90 days post surgery	At progression /recurrence	Follow up after progression /recurrence
		W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12					
		(Each cycle = 21 days)																
SCANS																		
CT scan chest, CT or MRI abdomen, CT or MRI pelvis with contrast (C)	X (E)													X		Every 12 weeks following surgery for years 1-2, , every 6 months for year 3, then annually in years 4-5		
SURGERY																		
Radical Cystectomy or Nephroureterectomy or Ureterectomy																X		
SPECIMEN SUBMISSION (see Section 15.1) (F)																		
Archival tissue		X																
Whole blood & buffy coat		X												X(D)		X		
Urine		X												X(D)				
Tissue from surgery																X		
TREATMENT																		
Gemcitabine		X	X		X	X		X	X		X	X						
Carboplatin		X			X			X			X							
Avelumab		X		X		X		X		X		X						

Click here for Footnotes

9.2 Arm B: Surgery Only

	PRE-REG	Within 6 weeks of registration	90 days post-surgery	At progression/ recurrence	Follow up after progression/recurrence
PHYSICAL					
History & Physical Exam	X	X	X		
Weight & Zubrod Performance Status	X	X	X		
Disease Assessment (A)	X		Every 12 weeks following surgery for years 1-2, every 6 months for year 3, then annually in years 4-5		Annually
Toxicity Notation	X	X	X		
Follow up after prog?					
LABORATORY					
Pregnancy test (urine or blood) in women of child-bearing potential	X				
Complete Metabolic Panel [B]	X				
Complete blood cell counts (Hb, hematocrit, WBC, ANC (absolute neutrophil count), platelet	X				
TSH, free T4	X				
SCANS					
CT scan chest, abdomen, pelvis with contrast (C)	X (E)		Every 12 weeks following surgery for years 1-2, , annually in years 3-5		
SURGERY					
Radical Cystectomy, Nephroureterectomy or Ureterectomy		X			
SPECIMEN SUBMISSION (see Section 15.1) (F)					
Archival tissue		X			
Whole blood & buffy coat		X (D)	X		
Urine		X (D)			
Tissue from surgery		X			

Click here for Footnotes

Footnotes for 9.1 and 9.2:

A CT/MRI abdomen and pelvis, and x-ray/CT chest
B CMP to include (at minimum): Bilirubin, AST and ALT, alkaline phosphatase, and serum creatinine
C Participants with renal dysfunction who cannot receive contrast are recommended to undergo CT chest without contrast and MRI abdomen and pelvis with gadolinium
D Collect prior to surgery
E Bone scan if high alkaline phosphatase or suspected bone pain
F With participant consent
G Submit Adverse Event form in Rave WEEKLY for the first cycle (3 weeks), for first 20 patients on Arm A

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Pathologic complete remission

Pathologic complete remission (pCR) is defined as absence of all disease in the surgical specimen from radical cystectomy, nephroureterectomy or ureterectomy as determined by the pathologist at the institution, i.e. ypT0N0 disease. Those without a surgical specimen will assume to be non-responders.

10.2 Event-free Survival (EFS)

Event-free survival is defined as the time from randomization to the first EFS event. For those who do not undergo surgery, event time will be assigned to the date of disease assessment that indicated surgery was no longer indicated or physician decision not to conduct the surgery.

An EFS event is defined as: any of the following events:

- Progression of disease during the neoadjuvant period for which surgical resection is no longer indicated.
- If surgery is attempted but gross resection is abandoned due to unresectable tumor.
- If surgery is possible, but not performed for other reasons.
- If surgery is completed with positive soft tissue margins.
- Post-surgical high grade upper tract or muscle invasive bladder cancer.
- Post-surgical distant recurrence (biopsy of indeterminate lesions should be performed when feasible).
- Death due to any cause.

10.3 Recurrence

Imaging intervals are every 3 months for 2 years, then annually in years 3-5. The date of recurrence is the time at which specific radiologic criteria are met. Recurrence can also be dated to the time of a positive biopsy, if available, or at the time of investigator-assessed clinical progression. When a radiologic and histopathologic diagnosis date are both available, the date of radiologic diagnosis is preferred, because biopsies are typically prompted by preceding radiologic findings.

10.4 **Performance Status**: Participants will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
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 housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Dose Limiting Toxicities (DTLs)

- Any death not clearly due to the underlying disease or extraneous causes
- Hy's law
- Neutropenic fever
- Any grade 3+ non-hematologic toxicity
- Grade 4+ neutropenia or thrombocytopenia >7 days
- Grade 3+ thrombocytopenia with bleeding
- Grade 3+ nausea/vomiting or diarrhea >72 hours with adequate antiemetic and other supportive care
- Grade 3+ fatigue ≥ 1 week
- Grade 3+ electrolyte abnormality that lasts >72 hours, unless the patient has clinical symptoms, in which case all grade 3+ electrolyte abnormality regardless of duration should count as a DLT. Grade 3+ amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT.
- All AEs of the specified grades should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.
- For patients with hepatic metastases, AST or ALT >8xULN or AST or ALT >5x ULN for ≥14 days
- Discontinuation of treatment should be considered if:
  - ALT or AST >8xULN
  - ALT or AST >5xULN for more than 2 weeks
  - ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
  - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

11.0 STATISTICAL CONSIDERATIONS

The primary objective of this open label comparative randomized phase II multicenter trial with 1:1 randomization is to compare pathologic complete response as the primary endpoint. A dynamic balancing algorithm will be used to randomize participants in a 1:1 ratio to the two arms based on the three stratification factors (clinical stage, performance status and creatinine clearance). All eligible, randomized participants will be assessed for the primary outcome regardless of amount of neoadjuvant treatment received in an ITT analysis. Those participants not undergoing protocol surgery will be assumed to be non-responders. With 178 evaluable participants, the trial will have a power of 90% (using a 1-sided alpha 0.05) to detect pCR rate improvement from 15% to 35%. This increment in pCR rate is hypothesized to be highly likely to translate to improved PFS and OS, given the results of SWOG **S8710**. To account for a 10% ineligible rate, the total accrual goal is 196 randomized participants.

11.1 Estimate of Sample Size and Accrual Rate

With 178 evaluable participants, the trial will have a power of 90% (using a 1-sided alpha 0.05) to detect pCR rate improvement from 15% to 35%. This increment in pCR rate is hypothesized to be highly likely to translate to improved PFS and OS, given the results of SWOG **S8710**. To account for a 10% ineligible rate, the total accrual goal is 196 randomized participants.

Based on accrual to previous SWOG neoadjuvant therapy and radical cystectomy focused bladder cancer trials (**S8710**, **S1314**, **S1011**), and the increased momentum behind the use of immunotherapy and neoadjuvant chemotherapy for muscle invasive bladder cancer, we anticipate an accrual rate of 8 participants per month. We anticipate full accrual will take 2.0 years.

11.2 Analysis Plan

There will be one safety and one futility interim analysis conducted when the first half of the participants have been enrolled and evaluated on both arms for pathologic response. If the complete pathologic response rate for the neoadjuvant therapy followed by surgery arm is smaller than that for surgery alone then we will conclude futility and close the study.

The safety analysis will be conducted in the first 20 patients on Arm A. These patients will be evaluated more intensively for adverse events, with AE assessment data submitted weekly for the first cycle (3 weeks). Although there will be a global approach to AE assessment, we will focus particularly on DLTs. If 7 (35%) or more of the first 20 evaluable patients on the experimental arm experience DLTs, then consideration will be given to reevaluating the safety and feasibility of the experimental regimen. Detailed listings of toxicities and supportive data will be evaluated by the study team, the study DSMC and CTEP.

The futility analysis will be conducted when the first half of the participants have been enrolled and evaluated on both arms for pathologic response. If the complete pathologic response rate for the neoadjuvant therapy followed by surgery arm is smaller than that for surgery alone then we will conclude futility and close the study.

The final analysis of the primary objective will be conducted after all participants have been evaluated for path response. A logistic regression model will be fit to path CR as the outcome and will include stratification factors as covariates in the model. If the one-sided p-value is less than or equal to 0.05 for the neoadjuvant treatment arm odds ratio then we will conclude a statistically significant result.

For the secondary event-free survival endpoint (see Section 10.0), with 89 eligible participants per arm, 2 years of accrual and 3 additional years of follow-up, and assuming a median EFS on the surgery alone arm of 24 months, which is expected based on the median disease-free survival on the control arm of the MRC trial *(2)*, the trial will also have power of 80% to detect an increase in the median EFS with the addition of the neoadjuvant regimen of 12 months, for a median of 36 months (equivalent to a hazard ratio of 0.667) using a one-sided alpha=0.10.

Timeline	Surgery Only	NAC + surgery	Statistical Power for EFS**	Type I Error Rate for EFS
Accrual completed	89 participants enrolled	89 participants enrolled		
Six months post-accrual	Analysis of primary objective, pT0 rate comparison between arms		N/A	N/A
	Median Assumed to be 24 months	Median Assumed to be 36 months		
1 year post-accrual completion	# of EFS events = 44	# of EFS events = 32	0.71	0.10
2 year post-accrual	# of EFS events = 57	# of EFS events = 44	0.79	0.10
3 years post-accrual	# EFS events = 66	# of EFS events = 53	0.84	0.10
** if primary EFS analysis conducted at the given time point.				

11.3 Adverse Event Monitoring

The study chair, statisticians and data coordinator(s) will review summary reports on a monthly basis which include adverse events by arm, treatment dose modifications, and reasons for discontinuation of protocol treatment. Serious adverse events are reviewed by the study team immediately after receiving notification. Additionally, the study chair will be reviewing patient data via our Study Chair Evaluation system on an ongoing basis throughout the study.

11.4 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG Cancer Research Network, three SWOG members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every six months from the SWOG Statistics and Data Management Center and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

There is no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Arm A: Initiation of systemic treatment must be planned to start no more than 14 calendar days after registration.

Arm B: Surgery must be planned to occur within 6 weeks after registration

13.2 Investigator/Site Registration

Prior to the recruitment of a participant for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

13.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register andwith their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP’s web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five-person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and appropriate RCR registrationby July 1, 2023 for all users) is required to access all CTEP and participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster
- Selection as the treating, credit, consenting, or drug shipment (IVR only) investigator or consenting person in OPEN Ability to be named as the site-protocol Principle (PI) on the IRB approval; and
- Assignment the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.govmailto:.

13.4 CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support System (RSS).Unit (CTSU) members' website.
This study is supported by the NCI CTSU.

a. **IRB Approval:**

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all applicable protocol-specific requirements (PSRs).

b. **Downloading Site Registration Documents:**

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);

- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *SWOG* and protocol number **S2011**.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

c. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with participants waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

d. **Checking Your Site's Registration Status:**

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

e. **Delegation of Task Log (DTL)**

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling participants to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

13.5 Oncology Patient Enrollment Network (OPEN) Registration Requirements

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of participant registration/randomization

assignment. OPEN will populate the participant enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to participant enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a participant transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.
Prior to accessing OPEN, site staff should verify the following:

- Participant has met all eligibility criteria within the protocol stated timeframes; and
- All participants have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.6 Exceptions to SWOG registration policies will not be permitted.

a. Participants must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL participants registered, whether or not assigned treatment is administered, including participants deemed to be ineligible. Participants for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol page on www.swog.org the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

d. Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data via direct links available in the DQP modules.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendar functionality.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS AFTER REGISTRATION:

Submit the following:

Vital Status form

Onstudy Forms

Documentation that participant is deemed a surgical candidate (uploaded as a source document in Rave)

Pathology Report from TURBT or ureteroscopic biopsy of the UTUC (upload as a source document in Rave)

Submit scan reports from all scans performed to assess disease at Pre-registration. (uploaded as source documents in Rave)

Blood and Urine specimens as outlined in Section 15.0

b. WITHIN 30 DAYS AFTER REGISTRATION:

Submit the following:

Archival tissue specimens as outlined in Section 15.0

c. WITHIN 7 DAYS FOLLOWING EACH OF WEEKS 1 – 3 (WEEKLY SUBMISSIONS IN CYCLE 1) - **FIRST 20 PATIENTS IN ARM A ONLY**

Vital Status Form

Adverse Event Form

Treatment Form (submit once, at the end of the cycle/week 3)

d. WITHIN 15 DAYS AFTER EACH CYCLE OF SYSTEMIC TREATMENT **(ARM A ONLY)**
* for the first 20 patients on Arm A, this section applies to cycles 2 and beyond

Submit the following:

Vital Status Form

Treatment Form

Adverse Event Form

e. WITHIN 15 DAYS AFTER DISCONTINUATION OR COMPLETION OF SYSTEMIC TREATMENT **(ARM A ONLY):**

Submit the following:

Vital Status Form

S2011 Off Systemic Treatment Notice

Final Treatment Form

Adverse Event Form

Blood and Urine specimens as outlined in Section 15.0

f. WITHIN 15 DAYS AFTER DECISION TO NOT PERFORM PROTOCOL SURGERY OR 8 WEEKS AFTER LAST NEOADJUVANT THERAPY (whichever occurs first) **ARM A ONLY**:

Vital Status Form

S2011 Surgery Status Form

g. WITHIN 15 DAYS AFTER DECISION TO NOT PERFORM PROTOCOL SURGERY OR 6 WEEKS AFTER REGISTRATION (whichever occurs first) **ARM B ONLY**:

Vital Status Form

S2011 Surgery Status Form

h. WITHIN 15 DAYS AFTER PROTOCOL SPECIFIED SURGERY **(ARMS A & B)**

Vital Status Form

S2011 Surgery Status Form

S2011 Surgery Reporting Form

Operative Report (uploaded as a source doc in Rave)

Pre-surgery blood and urine specimens as outlined in Section 15.0

i. WITHIN 30 DAYS AFTER PROTOCOL SPECIFIED SURGERY **(ARMS A & B)**

Surgical tissue specimens as outlined in Section 15.0

j. WITHIN 15 DAYS AFTER 90-DAY POST-SURGERY ASSESSMENT **(ARMS A & B)**

Vital Status Form

S2011 90 Day Post-Surgery Form

Adverse Assessment form

Blood specimen as outlined in Section 15.0

k. WITHIN 30 DAYS AFTER EACH DISEASE ASSESSMENT UNTIL PROGRESSION:

Submit the following:

Vital Status Form

Follow Up Form

Submit scan reports from all scans performed to assess disease. (uploaded as source documents in Rave)

l. WITHIN 15 DAYS OF PROGRESSION/RELAPSE:

Vital Status Form

Follow-Up Form (documenting date, site and method for determining progression/relapse).

m. FOLLOWING PROGRESSION, Within 30 days of EVERY Follow-up (Annually until 5 years from registration)

Submit the following:

Vital Status Form

Follow Up Form

Late Adverse Events (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the participant experiences any severe [Grade ≥ 3] adverse event that is possibly, probably, or definitely related to protocol treatment, or a Serious Adverse Event [SAE] of any grade/attribution, that has not been previously reported).

n. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and a final** Follow-Up Form documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for Banking **(REQUIRED with Participant Consent)**

Specimens for banking (submitted to the SWOG Biospecimen Bank–Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (Optional for Participants):

With participant consent, the following specimens must be submitted.

a. Formalin-fixed paraffin embedded (FFPE) tissue

1. Submitted at the following timepoints:

- Tumor tissue from baseline (archival) transurethral resection of bladder tumor (TURBT) or upper tract biopsy from endoscopic biopsy for all participants must be submitted within 30 days after registration.

- Tissue from radical cystectomy, nephroureterectomy, or ureterectomy must be submitted within 30 days after surgery.

2. FFPE Tissue Specimen Collection and Submission Instructions
   - Submit either:
     - One (1) block with tumor tissue **or**
     - One (1) H&E slide from each source block and ten (10) 4 μm unstained tissue on charged slides and five (5) 10 μm unstained tissue on uncharged slides. If slides are limited, we prefer prioritization of the 10 μm unstained slides. We appreciate that for TURBT or upper tract biopsy, this tissue may be limited.

   - Blocks or slides must be shipped at ambient temperature.

   - Refer to the tissue labeling and submission instructions on the SWOG Specimen Submission webpage:

   - (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

   - Specimen collection kits are not provided for this submission; sites will use institutional supplies.

b. Whole blood & Buffy Coat

1. Submitted at the following timepoints:

Arm A
- Prior to start of systemic treatment
- After end of systemic treatment, prior to surgery
- 90 days post surgery

Arm B
- Prior to surgery
- 90 days post surgery

2. Blood Collection and Submission Instructions

- Draw one (1) 10mL EDTA (lavender top) tube at each time point
- Draw one (1) 10 mL green-top (heparin) tube blood at each time point: 10 ml must be collected into a heparin tube at the specified time points. Blood should be processed for buffy coat as outlined on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources) and stored at -70º C until shipped. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.
- Follow packaging and shipment instructions on the SWOG specimen Submission webpage located at the following URL: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures
- EDTA tubes and green-top (heparin) tubes may be batch shipped on dry ice (every 3 months)

3. Streck Tube (10 ml) at each time point

- Streck tubes will be provided by the study. Immediately after patient registration, order a ctDNA Streck tube kit via the following URL: https://kits.bpc-apps.nchri.org . Orders placed by noon Eastern should be received within 3-4 business days.

NOTE: Streck tubes cannot be frozen and should not be batch shipped.

c. Urine

1. Submitted at the following timepoints:

Arm A
- Prior to start of systemic treatment
- After end of systemic treatment, but prior to surgery

Arm B
- Prior to surgery

2. Urine collection and submission instructions

- Collect 50 ml urine
- Aliquot collected urine into 15 cc conical tubes, centrifuge 10 minutes at 1,000 g (4ºC)
- Split pellet and supernatant into separate conical tubes and then freeze (-80 ºC) until shipment.

Urine may be batch-shipped every 3 months on dry ice. Ship to the SWOG Biospecimen Bank – Solid Tissue (Lab #201).

15.2 SHIPPING SAMPLES

a. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system must be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The participant ID must be included on any source documentation included with the shipment.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org); or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

b. Federal guidelines for the shipment of blood products:

1. The tube must be wrapped in an absorbent material.

2. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and tube in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. Mark the box "Biohazard".

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations. The model consent forms created for this study were modeled after the NCI informed consent template.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the

Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

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

The provision of Avelumab at no cost by EMD Serono / Merck KGaA for this study does not constitute an inducement to recommend, prescribe, purchase, or administer any of their products.

Monitoring

*For studies assigned **Demography** monitoring **and** enrolling patients via **OPEN**:*

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

Personal information of Study personnel may be transferred outside of the United States by the industry funder, EMD Serono, and held or processed by Affiliates of EMD Serono R&D. Affected individuals may have rights afforded under the EU – GDPR regulations. Further information about these rights can be obtained by contacting Privacy@emdgroup.com

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Document

18.0 Appendix

18.1 New York Heart Association Functional Classification

18.2 Patient Clinical Trial Wallet Card

18.3 Instructions for Biospecimen Bank

18.1 New York Heart Association Functional Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

18.2 Patient Clinical Trial Wallet Card

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

Version *mmm/yyyy*

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

18.3 Instructions for BioSpecimen bank

a. Tissue

- FFPE unstained slides from pre-study TURBT. The slides will be stored in a -20°C freezer after accession and barcoding.
- FFPE unstained slides from radical cystectomy, nephroureterectomy, or ureterectomy. Upon receipt, the Bank will accession, barcode, and store FFPE slides in a -20°C freezer. If a block is received, it will be barcoded and stored at room temperature for future sectioning. The block will not be returned per SWOG policy unless written request is received. 10 slides will be cut before return of the block.

b. Blood:

- Whole blood in EDTA tube: Upon receipt, the Bank will isolate plasma and bank in 1 ml aliquots, in a -80°C freezer until distribution.
- Blood in Streck cfDNA tubes: Buffy coat and plasma are processed from blood in Streck cfDNA tubes. Plasma is processed following a double-centrifugation protocol. Aliquots of plasma are stored in a -80°C freezer.
- Blood in sodium heparin: Buffy coat is processed from blood in a heparin tube and stored in a -80°C freezer.

c. Urine

- Urine: Upon receipt, the bank will accession, barcode the frozen pellet and supernatant aliquots, and store them in a -80°C freezer.

The Bank will retain all specimens until CTEP approves use of the specimens for translational medicine studies.