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Activation Date February 7, 2017

SWOG

PHASE II TRIAL OF ATEZOLIZUMAB IN BCG-UNRESPONSIVE NON-MUSCLE INVASIVE BLADDER CANCER

This is an FDA Registration Trial. Additional site requirements include maintenance of a Trial Master File (https://www.swog.org/sites/default/files/docs/2017-10/Guidance on FDA Inspection.pdf) and additional monitoring (see Appendix 18.2).

NCT #02844816

STUDY CHAIRS:

Principal Investigator:
Peter C.V. Black, M.D. (Urology)
BC Cancer Agency - Vancouver Centre
600 West 10th Avenue
Vancouver, BC V5Z 4E6
Phone: 605/875-4301
Fax: 604/875-5677
E-mail: pblack@mail.ubc.ca

Parminder Singh, M.D. (Medical Oncology)
Mayo Clinic Arizona
5881 E. Mayo Boulevard
Phoenix, AZ 85054
Phone: 480/342-4800
Fax: [redacted]
Email: Singh.Parminder@mayo.edu

Seth P. Lerner, M.D. (Urology)
Scott Department of Urology
Baylor College of Medicine
7200 Cambridge
Houston, TX 77030
Phone: 713/798-6841
Fax: [redacted]
E-mail: slerner@bcm.edu

TRANSLATIONAL STUDY [redacted]:

[redacted], Ph.D.
Johns Hopkins Greenberg Bladder Cancer Institute
Brady Urological Institute at Johns Hopkins
600 North Wolfe Street,
Marburg Building / [redacted]
Baltimore, MD 21287-2101
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

AGENTS:

NCI Supplied Investigational Agents
[redacted]
Atezolizumab (NSC # 783608)

PATIENT ADVOCATE:

[redacted]
Phone: [redacted]
E-mail: [redacted]

BIOSTATISTICIANS:
[redacted] Dr.P.H. (Biostatistics)
[redacted], Ph.D. (Translational Studies)
[redacted], M.S.
SWOG Statistics and Data Management Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: [redacted]
Fax: 206/667-4408
E-mail: [redacted]
E-mail: [redacted]
E-mail: [redacted]

PATHOLOGY STUDY [redacted]:

[redacted], M.D.
University of Colorado HSC
Department of Pathology, Mail Stop 8104
12801 East 17th Avenue, Rm L18-5103
P.O. Box 6511
Aurora, CO 80045
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

CCTG [redacted]:

[redacted] M.D.
McGill University Health Center
1001 Decarie Blvd, D02.7210
Montreal QC H4A 3J1
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

ALLIANCE [redacted]:

Sima Porten, M.D.
University of California San Francisco
Department of Urology
550 16th Street, 6th Floor
San Francisco, CA 94143
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

ECOG-ACRIN [redacted]:

[redacted] M.D., Ph.D.
Johns Hopkins University
600 N. Wolfe Street, Marburg 409
Baltimore, MD 21287
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology
CCTG/Canadian Cancer Trials Group
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG
CCTG/Canadian Cancer Trials Group

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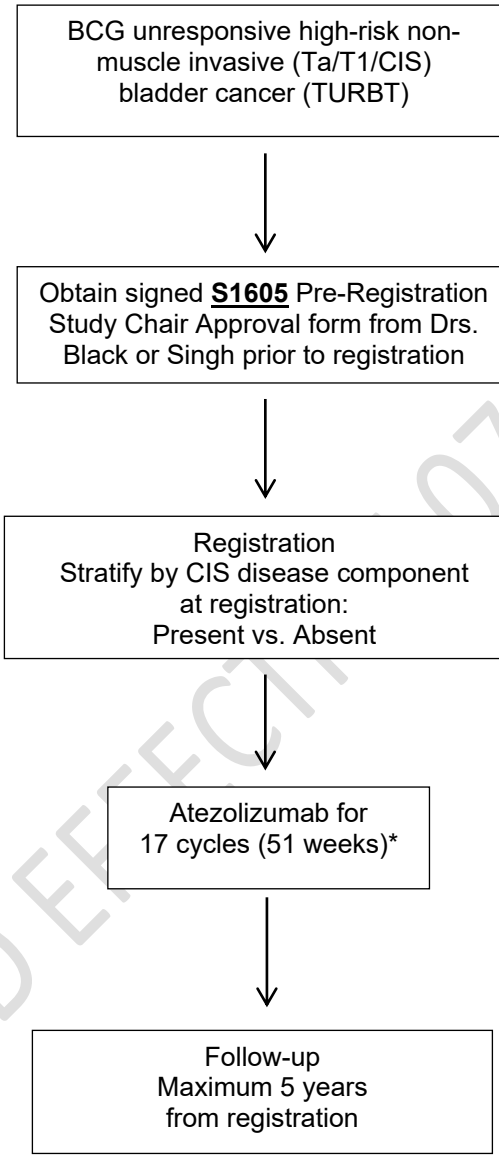
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study 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 Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at 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 user log on with CTEP-IAM username and password.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center by phone or email: 206/652-2267 guquestion@crab.org **For treatment or toxicity related questions** contact the Study Chair by phone or email: (Dr. Peter C.V. Black at 605/875-4301)		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA



* Cystoscopy and cytology performed as specified in the study calendar (see Section 9.0). Mandatory biopsy at Week 25 for patients with any CIS component.

1.0 OBJECTIVES

1.1 Primary Objective(s)

a. To estimate complete response at 25 weeks after registration for those with a CIS component and to evaluate event-free survival at 18 months in patients with BCG-unresponsive high-risk non-muscle invasive bladder cancer (Ta/T1/CIS) treated with atezolizumab.

1.2 Secondary Objective(s)

a. To estimate event-free survival at 18 months for the subset of patients with papillary cancer (Ta/T1).

b. To estimate progression-free survival, cystectomy-free survival, bladder cancer-specific survival, overall survival in all patients.

1.3 Additional Objective(s)

a. To estimate the level of agreement between local and central pathology review in terms of recurrence (for all patients) and complete response (for the CIS subset).

b. To identify markers that predict response to atezolizumab in the CIS population and that are associated with EFS in patients with Ta/T1/CIS BCG-unresponsive non-muscle invasive bladder cancer. The following markers will be tested:

- Expression of PD-L1 and CD8 by immunohistochemistry (IHC)
- Expression of immune signatures by RNA-sequencing (RNA-seq)
- Peripheral immune response by mass cytometry (CyTOF) and TruCulture

2.0 BACKGROUND

Defining the Clinical Unmet Need

Bladder cancer is a common malignancy with over 75,000 new cases diagnosed every year in the United States. *(1)* Seventy percent or more of these patients are diagnosed at an early stage with non-muscle invasive bladder cancer (NMIBC). Around 15-20% of these patients are at high risk (30-40%) of progression to muscle invasive bladder cancer (MIBC), which has a significant negative impact on survival. *(2)* Patients with high-grade Ta or T1 papillary disease or carcinoma in situ (CIS) constitute the majority of these high-risk patients. *(3)*

For the past 35 years the standard of care for patients with high-risk NMIBC has been complete transurethral resection (biopsy only for CIS) followed by intravesical immunotherapy with Bacillus Calmette-Guerin (BCG). *(4)* Although 75-80% patients will have an initial complete response in the case of CIS with or without papillary disease, or be free of recurrence six months from initiating treatment, at least one third of these patients will recur. *(5)* Some patients may be treated effectively with additional BCG with or without interferon, but a third course of BCG is regarded as ineffective. *(6)* Cookson and colleagues reported that 53% of high-risk patients ultimately progressed to cystectomy or died from their disease with 15-year median follow-up. *(7)*

In a randomized Phase II trial of BCG unresponsive patients, 80 subjects were randomized to gemcitabine versus repeat BCG. *(8)* At two years, recurrence free survival was 19% in the gemcitabine arm and 3% in the BCG arm ($p < 0.008$). Thirty-three percent in the gemcitabine arm and 37.5% in the BCG arm had progression of disease and underwent radical cystectomy. This study validates the expert consensus that trials in BCG-unresponsive patients should not include a control arm consisting of BCG alone. *(9,10,11)*

Valrubicin is the only FDA approved treatment for BCG unresponsive CIS. *(12)* A single arm Phase II study evaluated the activity of intravesical valrubicin in 90 patients with carcinoma in situ who had failed prior BCG with or without other subsequent intravesical therapies. The trial demonstrated a 21% complete response rate at six months and only 8% disease-free rate at 30 months. Life table analysis on the data from this trial demonstrated that the likelihood of being disease free at 12 months was only 17%. *(13)* This trial led to the approval of valrubicin by the FDA for this indication. This trial exemplifies the precedence of drug approval in this setting based on Phase II data.

In a SWOG-led single arm Phase II clinical trial, **S0353**, 58 patients were enrolled to test the activity of intravesical gemcitabine induction followed by maintenance in patients with BCG unresponsive NMIBC. Eligible patients had recurrent NMIBC following two induction courses of BCG (6+6) or induction plus at least one maintenance cycle (6+3). Forty-seven patients were evaluable for response. At three months and two years, 47% and 21%, respectively, were free of recurrence. The trial demonstrated the activity of intravesical gemcitabine; however, the poor durability of response with maintenance therapy emphasizes the need for newer treatment options. *(14)*

Intravesical chemotherapy with other agents, including mitomycin, docetaxel, or doxorubicin is considered inferior to BCG therapy in high-risk disease, and its efficacy in the second line setting is uniformly poor with two-year recurrence- free survival rates typically below 20%. *(15)* Radiation is only rarely administered for high-grade T1 disease, although there is an ongoing clinical trial evaluating the efficacy of this approach (RTOG 0926).

In patients who progress to muscle invasive disease, the bladder cancer specific death rate at 10 years has been reported to be approximately 50%. *(16)* Radical cystectomy is therefore considered the standard of care for any patient with BCG-unresponsive high-grade NMIBC. *(17)* Even in the best surgical hands this procedure entails high morbidity (up to 60%) and risk of mortality (2.7 to 9%). *(18,19)* Many patients are medically unfit for cystectomy and others refuse the surgery. In all cases cystectomy has a significant impact on quality of life. There is thus an urgent need for new treatments that offer these patients the opportunity to preserve their bladders with an acceptably low risk of progression.

Rationale for Checkpoint Inhibition in High-Risk Non-Muscle Invasive Bladder Cancer

Intravesical BCG has demonstrated modest efficacy in preventing recurrence and progression to muscle invasive bladder cancer (MIBC). While the mechanism of action of BCG has not been fully elucidated, the need for an intact immune system is well recognized. When NMIBC becomes refractory to BCG, the implication is that the disease is able to evade the BCG-induced immune response. Recent evidence in tumor-mediated immune evasion has highlighted the negative immune checkpoint termed programmed death (PD)-1. Blockade of the PD-1 axis mediates anti-neoplastic activity by promoting effector function of tumor infiltrating immune cells, which recognize cancer neoantigens as foreign but are maintained in an anergic state via negative co-signaling from the immune checkpoint expressed in the malignant milieu, expressed on both immune cells and tumor cells themselves (the cancer-immunity cycle). *(20.21)*

Strong clinical evidence is mounting for efficacy of monoclonal antibody blockade of either PD-1 or its ligands (PD-L1 and PD-L2) in patients with advanced urothelial carcinoma of the bladder and upper urinary tract. In particular, the anti-PD-L1 antibody atezolizumab (Genentech) was recently approved by the FDA for second-line therapy after prior cisplatin-based chemotherapy in patients with advanced urothelial carcinoma.

Breakthrough status for atezolizumab was initially granted by the FDA based on results from a large Phase I trial with an adaptive design that included an expansion arm of 68 patients with pre-treated metastatic urothelial carcinoma. *(22)* These results were subsequently updated at ASCO 2015. *(23)* An objective response was observed in 43% (46% in update) of patients with high expression of PD-L1 in their tumor infiltrating immune cells, compared to 11% (16% in update) in patients with low expression. Complete response was observed in 7% of patients, all of whom had high PD-L1 expression. The drug was well tolerated with only 3% of patients experiencing Grade

3-4 toxicities (8% in update), which were predominantly asthenia, thrombocytopenia, and electrolyte abnormality. (24)

Results from a Phase II clinical trial of atezolizumab in patients with metastatic urothelial carcinoma progressing on cisplatin-based chemotherapy were published more recently. *(25)* Of 311 patients included on the trial, 100 were considered positive (2-3+) for PD-L1. The overall response rate (ORR) was 15% for the entire cohort and 26% for the positive patients. Thirty-eight of 45 (84%) responding patients were still responding to therapy at the time of data cut-off. Grade 3-4 adverse events were observed in 16% of patients. A large (767 patient) multicenter Phase III trial with the same agent has completed accrual in the metastatic setting after prior failure of cisplatin-based chemotherapy, but has not yet been reported.

A third trial tested the PD-1 inhibitor pembrolizumab in the same setting with similar results. *(26)* Only patients with PD-L1 expression were included, and the ORR was 25% in 28 evaluable patients. Avelumab, another PD-L1 inhibitor, was tested in a Phase 1b trial in 129 unselected patients with metastatic or locally advanced urothelial carcinoma; the ORR was 16.5%. *(27,28)* PD-L1 expression in tumor-infiltrating immune cells in bladder tumors has been predictive of ORR in these trials. Nivolumab, another PD-1 inhibitor, showed comparable results in an early report in the metastatic setting. *(29)*

The first Phase III data for checkpoint blockade in urothelial carcinoma has not yet been reported, but October 21, 2016 Merck announced that their randomized Phase III trial comparing pembrolizumab to investigator's choice chemotherapy (Keynote 045 Trial) in the second line for patients with metastatic urothelial carcinoma was halted early due to superiority of the pembrolizumab arm. *(30)*

Two studies have demonstrated that PD-L1 is also expressed in NMIBC. An analysis by Inman et al. included 44 BCG-treated patients with NMIBC, of whom 16 developed recurrent disease. The initial TNM stages of these 16 patients were pTa in 10 cases, pT1 in 3 cases, and CIS in 3 cases. Only three of these patients were PD-L1-positive in the original tumor specimen, but 12 of the 16 recurrences had BCG granulomata, and 11 of these granulomata showed a pattern of diffuse and intense (> 90% of cells) PD-L1 staining. Hurwitz et al. measured PD-L1 expression in a cohort of 39 patients who underwent at least two transurethral resections of bladder tumor (TURBT) for first and recurrent NMIBC, of whom 23 received intravesical BCG between the first and second TURBT. PD-L1 was detected in seven of 39 patients with first TURBT, 12 of 39 with second TURBT, and seven of 13 with third TURBT. The authors concluded that PD-L1 expression was associated with the number of recurrences, but not with BCG therapy. *(31,32,33)*

Checkpoint inhibitors have been studied in pre-clinical models of NMIBC. Mangsbo et al. have tested combined inhibition of anti-CTLA4 with either anti-PD-L1 or anti-PD-1 in a syngeneic model of NMIBC. *(34)* These agents caused an increase in tumor-reactive T-cells in circulation and a decrease in regulatory T-cells in tumor tissue, which was reflected in clear inhibition of tumor growth and improved mouse survival. Avelumab (anti-PD-L1) similarly inhibited tumor growth and improved mouse survival in a recent presentation by Vandeveer et al. *(35)* Finally, de Boisferon et al. observed better efficacy of systemic PD-1 inhibition compared to intravesical BCG in a syngeneic mouse model. *(36)*

Blockade of the PD-1 axis in high-grade NMIBC (Ta, T1, and CIS) has not been investigated to date. The best clinical data on the use of checkpoint inhibitors in NMIBC is derived from a small trial that tested ipilumimab (CTLA4 inhibitor) in 12 patients with T1 and T2 bladder cancer prior to radical cystectomy. *(37)* The primary endpoints of this trial were safety and immune monitoring. The expression of ICOS ("inducible costimulator") in $CD4^+$ T-cells is considered a pharmacodynamic marker of ipilumimab effect. All patients had an increased frequency of $CD4^+/ICOS^{hi}$ T-cells in both tumor tissues and in the peripheral blood. These $CD4^+/ICOS^{hi}$ T cells produced IFN-gamma and were shown to recognize tumor antigen (NY-ESO-1). There was an increase in the ratio of effector to regulatory T-cells.

Correlative Markers

The translational component of this proposal focuses on identification of predictive markers of response to anti-PD-L1 therapy.

Virtually every early trial testing a checkpoint inhibitor in metastatic bladder cancer has found that response rates are highest in patients with high expression levels of PD-L1 by immunohistochemistry (IHC). This holds true also in the Phase I and II trials of atezolizumab after prior cisplatin-based chemotherapy. *(38,39)* Furthermore, CD8 expression measured by IHC, which is a marker of cytotoxic T-cell infiltration, also correlates to response. We will test both IHC markers in our patient cohort at baseline and with every subsequent mandatory or for-cause biopsy.

Early phase trials show also that gene expression signatures can predict response to atezolizumab. These signatures include proprietary immune signatures developed by Genentech, but also the molecular subtypes described by The Cancer Genome Atlas (TCGA). *(40)* The TCGA describes four clusters that are being referred to increasingly as luminal 1 and 2, and basal 1 and 2. The phase II trial of atezolizumab in second-line metastatic urothelial carcinoma revealed that patients with luminal 2 (also known as "immune infiltrated luminal") subtype have the highest rate of response. Basal 2 tumors (with even higher immune infiltration) have intermediate response, and luminal 1 and basal 1 tumors demonstrate a low response rate. A recent paper confirmed that the same molecular subtypes can be found also in NMIBC. We will test the immune signatures and subtypes in our cohort of BCG unresponsive high risk NMIBC patients and correlate these to response to therapy. For further details see Section 18.1.

Inclusion of Women and Minorities

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	0	0	0	0
Asian	3	9	0	0	12
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	11	16	0	0	27
White	42	92	4	3	141
More Than One Race	0	3	0	0	3
Total	56	120	4	3	183

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	1	0	0	1
White	6	11	0	0	17
More Than One Race	0	0	0	0	0
Total	6	13	0	0	19

3.0 DRUG INFORMATION

Investigator Brochures

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

For this study, atezolizumab is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator Brochure may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 240/276-6575.

3.1 Atezolizumab (NSC # 783608) (IND #TBD)

a. PHARMACOLOGY

Mechanism of Action: Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on immune cells or tumor cells and prevents interaction with either programmed death-1 (PD-1) receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function. By eliminating Fc-effector function and antibody dependent cell-mediated cytotoxicity (ADCC), antibody-mediated clearance of activated effector T cells is also eliminated. Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients, and is being investigated as a potential therapy in a wide variety of malignancies.

b. PHARMACOKINETICS

On the basis of available preliminary PK data (0.03-20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent CL and the mean Vss had a range of 3.20 to 4.44 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

Serum atezolizumab concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase. Atezolizumab exhibited nonlinear pharmacokinetics at doses <1 mg/kg (i.e., 0.03-0.3 mg/kg), likely due to target-mediated CL at lower concentrations. Atezolizumab exhibited linear pharmacokinetics at doses ≥ 1 mg/kg. At doses ≥ 1 mg/kg, the mean Cmax increased in a dose-proportional manner and was 26.0 mcg/mL for the 1-mg/kg dose group and 472 mcg/mL for the 20 mg/kg dose group. Similarly, at doses ≥ 1 mg/kg, the group mean AUC0-∞ had a range of 340-6050 Day x mcg/mL for 1 mg/kg and 20 mg/kg dose group and was approximately dose proportional, by similar CL across the dose range. The observed CL and Vss for atezolizumab at doses ≥ 1 mg/kg are consistent with these of a typical IgG1 antibody in humans.

Currently available PK and ATA data from Study PCD4989g suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain trough concentration (Ctrough) ³ 6 mg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed Ctrough data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted Ctrough levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg has been selected when atezolizumab is administered q3w (equivalent to an average body weight-based dose of 15 mg/kg). For the every-2-weeks (q2w) dosing interval used in this study, the corresponding fixed dose is 800 mg.

Refer to the atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of atezolizumab.

c. ADVERSE EFFECTS

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL3280A, NSC 783608)

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 3,097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

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 2.2, July 23, 2018[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Endocrine disorders - Other (diabetes)[2]	
	Hyperthyroidism [2]		
		Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
	GGT increased[2]		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Myasthenia gravis[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		

*Denotes adverse events that are < 3%.

[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] Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, 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 atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

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

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) 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.

1. Pregnancy and Lactation: No developmental or reproductive toxicity studies have been conducted with atezolizumab as several nonclinical studies have already demonstrated that the PD-L1/PD-1 signaling pathway is essential in establishing maternal/fetal tolerance, which is necessary for embryo-fetal survival during gestation. Based on the critical role that PD-L1/PD1 pathway plays in the maintenance of maternal-fetal

tolerance, atezolizumab should not be administered to pregnant women. The effects of atezolizumab on human reproduction or on the fetus or the developing infant are unknown but expected to have an adverse effect.

It is not known whether atezolizumab is excreted in human milk. However, antibodies are known to cross the placenta and are excreted in breast milk during lactation. Atezolizumab should not be administered to nursing mothers.

2. Drug Interactions: Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

d. DOSING & ADMINISTRATION

1. See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

1. Atezolizumab will be supplied free of charge. It will be provided by Genentech and distributed by CTEP PMB.

2. Atezolizumab is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

Atezolizumab vial size	**Vial volume**	**Final concentration**
1200 mg	20 ml	60 mg/mL

f. STORAGE, PREPARATION & STABILITY

Atezolizumab must be refrigerated at 2°C-8°C (36°F- 46°F) upon receipt until use. No preservative is used in atezolizumab and therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Atezolizumab (1200 mg per vial) will be administered in 250 mL 0.9% NaCl IV infusion bags and infusion lines equipped with 0.2 µm in-line filters. The IV bag may be constructed of polyvinyl chloride (PVC) or polyolefin (PO); the IV infusion line may be constructed of polyvinyl chloride (PVC) or polyethylene (PE); and the 0.2 mcm in-line filter may be constructed of polyehersulfone (PES). The use of administration supplies composed of materials other than those listed should be avoided if possible. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user.

The dose solution prepared for IV bag delivery may be stored at 2°C to 8°C (36°F to 46°F) and/or at room temperature for up to a total in-use storage time of 8 hours.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Atezolizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 and a CV. If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application https://eapps-ctep.nci.nih.gov/OAOP/. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers returns or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or e-mail PMBAfterHours@mail.nih.gov any time.

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 of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov)

a. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

b. Drug Return and/or Disposition Instruction

i. Drug Returns: All unused drug supplies should be recovered to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

ii. Drug expiration: (If packaging does not have expiration date, check with drug ordering designee and/or PI at site to confirm receipt of ongoing stability testing letter from NCI. If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first)

c. Contact Information

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

4.0 STAGING CRITERIA

PRIMARY TUMOR (T) (AJCC Seventh Edition, 2009)

Ta	Non-invasive papillary carcinoma
CIS	Carcinoma *in situ*: "flat tumor"
T1	Tumor invades subepithelial connective tissue

HISTOLOGIC GRADE (G)

WHO 2004/ISUP
Low-grade
High-grade

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or guquestion@crab.org prior to registration.

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 3 weeks later would be considered Day 21. This allows for efficient patient scheduling without exceeding the guidelines. If Day 21 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

5.1 Study Chair Approval Requirement

Patients' disease related criteria (Section 5.2) and BCG-unresponsiveness (Section 5.3a) must be discussed with at least one of the **S1605** Study Chairs prior to registration. The **S1605** Pre-Registration Study Chair Approval form must be signed by one of the **S1605** Study Chairs to indicate approval within 30 days prior to registration.

The **S1605** Pre-Registration Study Chair Approval Form is located in Section 18.4. See Section 14.4a for form submission requirements.

5.2 Disease Related Criteria

a. Patients must have histologically proven, recurrent, non-muscle invasive urothelial carcinoma of the bladder within 60 days prior to registration. The carcinoma must be Stage T1 High-Grade, Stage CIS, or Stage Ta High-Grade (see Section 5.2f for high-grade T1).

b. Patients with mixed urothelial carcinoma and a glandular and/or squamous component will be eligible for the trial, but the presence of other histologic variants, pure adenocarcinoma, or pure squamous cell carcinoma, or pure squamous carcinoma in situ will make a patient ineligible.

c. Patients must have had all visible tumor resected completely within 60 days prior to registration. CIS disease is not expected to be completely excised. All patients must have tumor tissue from the histologic diagnosis of recurrence (see Section 5.2.a) available for central pathology review submission (see Section 12.0). Failure to submit these materials will make the patient ineligible for this study.

d. Patients must have had cystoscopy confirming no visible papillary tumor within 21 days prior to registration. (CIS disease is not expected to have been completely excised). If the TURBT or bladder biopsy falls within 21 days of registration it will fulfill this criterion.

e. Patients must have had urine cytology within 21 days prior to registration. Cytology for patients with CIS component is not expected to be negative for malignant cells. If the cytology for male patients with only Ta/T1 disease in the absence of CIS is positive for malignant cells, patient must have had a biopsy of the prostatic urethra within the previous six months.

f. All patients with T1 urothelial carcinoma at study entry must undergo re-TURBT within 60 days prior to registration, and must have evidence of uninvolved muscularis propria in the pathologic specimen from either the first or the second TURBT. Tissue from the re-resection must be submitted for central review in addition to the tissue from the first TURBT (see Section 12.0). The TURBT that identified the recurrent T1 disease may have taken place more than 60 days prior to registration but not more than 120 days. Patients with high grade Ta or CIS do not require a re-TURBT, but if this is performed at the discretion of the treating physician, the second TURBT must be within 60 days of registration. There is no requirement for muscularis propria in the specimen of Ta/CIS patients, but the tissue from the first and second TURBTs must be submitted for central review. If a patient with Ta/T1 disease undergoes repeat TURBT, the patient will be stratified as having CIS if there is CIS on either TURBT.

g. Patients must not have had urothelial carcinoma in the prostatic urethra within the previous 24 months or muscle invasive urothelial carcinoma of the bladder at any time. Patients with prior urothelial carcinoma in the upper urinary tract within the previous 24 months will only be eligible if they had ≤ T1 carcinoma and were treated with nephroureterectomy. Patients must have a CT or MRI (including CT-

IVP, CT-urogram or MR-urogram) of the abdomen and pelvis to rule out upper tract malignancy and intra-abdominal metastases within 90 days prior to registration. If a patient cannot tolerate intravenous contrast, a retrograde pyelogram should be performed within 90 days prior to registration.

h. Patients must be deemed unfit for radical cystectomy by the treating physician, or the patient must refuse radical cystectomy, which is considered standard of care for these patients. The reason for patients not to undergo cystectomy will be clearly documented.

5.3 Prior/Concurrent Therapy Criteria

a. Patients must be BCG-unresponsive. A patient is BCG-unresponsive if they meet one or more of the following criteria:

- Patient has persistent or recurrent high-grade Ta/CIS urothelial carcinoma after completing therapy with at least induction BCG (≥ 5 doses) and first round maintenance (≥ 2 doses) or second induction BCG (≥ 2 doses). Both rounds of BCG must have been administered within a 12 month period. These patients must have either had high-grade Ta tumors and did not achieve a disease-free state for more than 6 months following last dose of BCG, or they had CIS and did not achieve a CR. **S1605** registration must occur within 9 months of the last dose of BCG.
    - If a patient does not meet these criteria only because the last dose of BCG was more than 9 months ago, the patient may become eligible if he/she shows histologically proven high-grade recurrence after an additional round of induction or maintenance BCG (≥ 3 doses) within 9 months prior to registration.
- Patient has persistent or recurrent high grade T1 urothelial carcinoma after completing therapy with at least induction BCG (≥ 5 doses). Patients with recurrent high grade T1 urothelial carcinoma after additional rounds of BCG will also be eligible, but one round of maintenance therapy or a second induction is not a pre-requisite for these patients. Trial registration must occur within 9 months of the last dose of BCG.
    - If a patient does not meet these criteria only because the last dose of BCG was more than 9 months ago, the patient may become eligible if he/she shows histologically proven high grade recurrence after an additional round of induction or maintenance BCG (≥ 3 doses) within 9 months prior to registration.
- Patient achieves disease-free state at 6 month time point (i.e., complete response; presence of only low-grade tumor at this timepoint is still considered complete response) after induction and maintenance (or second round of induction) BCG but later experiences a high-grade Ta/T1recurrence (with or without concomitant CIS) within 6 months after the last dose of BCG or recurrent CIS (in absence of concomitant Ta/T1 tumor) within 12 months after the last BCG dose. The time of eligibility is measured from the last dose of BCG to the time of disease recurrence. The patient must be registered on the trial within 60 days of this recurrence, or within 60 days of a re-TURBT if indicated. See Section 5.2f for TURBT requirements.

b. All adverse events associated with any prior surgery and intravesical therapy must have resolved to Grade ≤ 2 prior to registration.

c. Patients must not have had prior systemic chemotherapy for bladder cancer or systemic immunotherapy, including, but not limited to interferon alfa-2b, high dose IL-2, PEG-IFN, anti-PD-1, anti-PD-L1, intra-tumoral. Patients must not have had vaccine therapies within 6 weeks prior to registration. Patients must not have received or be planning to receive any of the prohibited therapies listed in Section 7.3 during protocol treatment. Prior intravesical administration of chemotherapy, interferon, Vicinium™ (VB4-845), BC-819 or Instiladrin™ (rAd-interferon-alpha/Syn3) is allowed if all other criteria are met and the last administration was ≥ 30 days before registration.

d. Patients must not be planning to receive concomitant other biologic therapy, radiation therapy, intravesical chemotherapy, surgery, or other anti-cancer therapy while on this protocol.

e. Patients must not have received any prior radiation to the bladder for bladder cancer.

f. Patients must not have received treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 4 weeks prior to registration. Exceptions: (1) Patients may have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea); (2) The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

g. Patients must not have received a live, attenuated vaccine within 4 weeks before registration or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of atezolizumab.

- Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

h. Patients must not require treatment with a RANKL inhibitor (*e.g.* denosumab) who cannot discontinue it before treatment with atezolizumab.

5.4 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500/ microliter (mcL); platelets ≥ 100,000/mcL; Hemoglobin ≥ 9 g/dL. These results must be obtained within 42 days prior to registration.

c. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL), and AST or ALT ≤ 2 x IULN. These results must be obtained within 42 days prior to registration.

d. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ 1.5 ULN OR measured or calculated creatinine clearance ≥ 30 mL/min. This result must have been obtained within 42 days prior to registration.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

e. Patients must have Zubrod Performance Status ≤ 2 (see Section 10.11).

f. Patients must have a baseline ECG performed within 42 days prior to registration.

g. Patient must not have history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis.

h. Patients must not have an active infection requiring oral or IV antibiotics within 14 days prior to registration. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

i. Patients must not have severe infections within 28 days prior to registration, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

j. Patients must not have active autoimmune disease that has required systemic treatment in past two years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Autoimmune diseases include, but are not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

k. Patients must not have undergone prior allogeneic bone marrow transplantation or prior solid organ transplantation.

l. Patient must not have active tuberculosis.

m. Patients must not have active hepatitis B (chronic or acute) or active hepatitis C infection.
- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

n. Patients positive for HIV are eligible only if they have all of the following:
a) A stable regimen of highly active anti-retroviral therapy (HAART)
b) No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
c) A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests.

o. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

p. Patients must not be pregnant or nursing due to the potential teratogenic side effects of the protocol treatment. Administration of atezolizumab may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of child-bearing potential and men must agree to use

adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of study agent. A woman is considered to be of "reproductive potential" if she has had a menses at any time in the preceding 12 consecutive months. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

q. Due to the potential drug reaction with atezolizumab, patients must not be known to be allergic to Chinese hamster egg or ovaries.

5.5 Specimen Submission Criteria

a. Patients must be offered the opportunity to participate in specimen banking for future studies, to include translational medicine studies as outlined in Section 15.0.

5.6 Regulatory Criteria

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

b. As a part of the OPEN registration process (see Section 13.3 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

CIS: Present vs. Absent (i.e., Ta/T1 only)

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. [redacted] at [redacted] or Dr. [redacted] at ([redacted]). For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

7.1 Pre-Medication

Premedication is not permitted for the first dose of atezolizumab. Premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician. See Section 7.2 for the management of Infusion Related Reactions.

7.2 Treatment

Patients will receive intravenous atezolizumab (1200 mg) once every 21 days for a total of 17 doses (cycles). Atezolizumab treatment may be administered up to three days before or after the protocol-specified dose administration date, each 21 day cycle, due to administrative reasons. Atezolizumab treatment will be administered on an outpatient basis.

Agent	Dose	Route	Days	Interval	Notes
Atezolizumab	1200 mg	Intravenous over 60 minutes	1	q 21 days	for a maximum of 17 cycles

(51 weeks)

Atezolizumab administration instructions:

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be monitored at the following timepoints during drug infusion:

- Before: Within 60 minutes of starting
- During: 15- 30 minutes after start
- After: At the end of infusion, within 30 minutes

No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

Premedication is not permitted for the first dose of atezolizumab. Premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician. The management of Infusion Related Reactions will be according to severity as follows:

- In the event that a patient experiences a Grade 1 Infusion Related Reaction during Cycle 1, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a Grade 2 Infusion Related Reaction, or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the Infusion Related Reaction. For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for Infusion Related Reactions
- For Grade 3 or 4, Infusion Related Reactions, the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Atezolizumab should be permanently discontinued. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event; retreatment requires consultation with the Study Chair.

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during atezolizumab infusion, the following procedures should be performed:

- Stop the study drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observation.

7.3 Disease Assessment

See Section 9.0 for disease assessment time points (approximately every 12 weeks). Disease assessment timing (cystoscopy, urine cytology, and biopsy) is to be based on calendar timing counted as weeks after registration, not based on cycles or drug administration.

Week 13:

Office cystoscopy and urine cytology will be performed 13 weeks after registration. Patients with suspicious cystoscopy or cytology findings positive for malignancy at 13 weeks (or at any other disease assessment time point) must undergo further evaluation with TURBT/biopsy, and patients with high-grade T1 or higher stage recurrences will be taken off protocol treatment. Persistent Ta or CIS at 13 weeks and low-grade recurrences at any timepoint will be tolerated without treatment interruption.

Only frankly malignant cytology (equivalent to Papanicolaou class V) will be considered "positive" and used to determine the need for bladder biopsy and further evaluation. Cytology is limited by its subjectivity and poor reproducibility so that lower grades of possible cytologic abnormalities cannot be used reliably. All patients will undergo close monitoring of the urine cytology, so that adverse changes will be noted promptly.
Week 25:

Complete response for patients with CIS component will be assessed with urine cytology, cystoscopy, and **mandatory** bladder biopsy at Week 25 (within ± 7 days of the start of Week 25, regardless of treatment delays). If patient is found to have persistent CIS or other high-grade disease, patient will be removed from protocol treatment. Patients with CIS at study entry achieving a complete response at 25 weeks will continue on protocol therapy as planned.

CIS patients with suspicious cystoscopy findings or cytology positive for malignancy at Week 13 and a negative biopsy at Week 13 are not required to undergo the mandatory Week 25 biopsy if their Week 25 cystoscopy is not suspicious and Week 25 cytology is negative for malignancy. A patient with positive cytology but negative biopsy at Week 25

must have re-evaluation of the upper tracts via CT or MRI (including CT-IVP, CT-urogram or MR-urogram) of the abdomen and pelvis (males and females) and biopsy of the prostatic urethra (males only).

Patients without CIS component at study entry (Ta/T1 only) will be assessed with cytology and cystoscopy. Patients with suspicious cystoscopy or cytology findings positive for malignancy at 25 weeks (or at any other disease assessment time point) must undergo further evaluation with TURBT/biopsy, and patients with any high-grade (Ta/T1/CIS) or higher stage recurrences will be taken off protocol treatment. Low-grade recurrences at any time point will be tolerated without treatment interruption.

Subsequent Disease Assessments:

For all patients, cystoscopic and cytologic monitoring will continue every 3 months for the first two years, then every six months for Years 3-5 until high-grade recurrence. Patients with suspicious cystoscopy or cytology findings positive for malignancy must undergo further evaluation with TURBT/biopsy.

Patients without evidence of a high-grade recurrence by 18 months (week 73) are required to have a CT or MRI at 18 months (week 73).

7.4 Prohibited and Cautionary Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phases of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- No systemic or intravesical use of any non-study anti-cancer agent (investigational or non-investigational).
- Investigational agents other than atezolizumab.
- Radiation therapy
- Live vaccines: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and **are allowed**; however, intranasal influenza vaccines (*e.g.* Flu-Mist®) are live attenuated vaccines, and are not allowed. Prior administration of intravesical BCG is allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids (defined as 10 mg prednisone) are acceptable, however site investigators should consult with the Study Chair for any dose higher than 10 mg prednisone.

7.5 Criteria for Removal from Protocol Treatment

a. High Grade T1 or greater at Week 13 or later

b. Recurrence of high-grade disease, muscle invasive or metastatic disease, or high-grade upper tract or urethral involvement (as defined in Section 10.0) at Week 25 or later.

c. Persistent CIS at Week 25 biopsy.

d. Unacceptable toxicity

e. Treatment delay > 84 consecutive days for any reason, except as specified in Section 8.0.

f. Completion of protocol treatment.

g. Pregnancy

h. The patient may withdraw from the study at any time for any reason.

i. The investigator may discontinue treatment if they determine that the patient's continued treatment on the study is detrimental to their long-term health, or due to poor compliance with the study's required visits and treatments.

7.6 Discontinuation of Treatment

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

7.7 Follow-Up Period

All patients will be followed for recurrence, progression, and survival for 5 years after registration.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov) All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Adverse Event Management and Dose Modification Guidelines

Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for >84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 additional weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Study Chair.

Atezolizumab must be permanently discontinued if the patient experiences any of the following events, regardless of benefit:

- Grade 4 pneumonitis
- AST or ALT >5×ULN or total bilirubin >3×ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis
- Grade 4 ocular inflammatory toxicity
- Grade 4 pancreatitis or any grade of recurrent pancreatitis
- Grade 4 rash
- Any grade myocarditis
- Grade 3 or 4 nephritis

Treatment may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events, but only after consultation with the Study Chair:

- Grade 3 pneumonitis
- Grade 3 ocular inflammatory toxicity
- Grade 3 or 4 infusion-related reactions

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al., 2010). Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of atezolizumab.

For detailed information regarding management of adverse events associated with atezolizumab, please refer to the most current version of the Atezolizumab Investigator's Brochure and the FDA product label.

The primary approach to Grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent Grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening irAEs.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Study Chair for additional recommendations.

8.3 Management of Specific AEs

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure. See Section 7.2 for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

Pulmonary events
Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the table below.

Endocrine disorders
Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including fatigue, myalgias, impotence, mental status changes, and constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Meningoencephalitis
Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines.

Neurologic disorders
Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies.

The table below presents management and dose modification guidelines for specific AEs. For recommendations to hold atezolizumab and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab therapy after resolution of the event:

- Corticosteroids must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Atezolizumab may be held for a period of time beyond 12 weeks (up to 4 additional weeks) to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
Abdominal pain	Acute abdominal pain	Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests. See the guidelines for “Amylase and/or lipase increase” and “Immune-related pancreatitis” elsewhere in this table, as needed. Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should be evaluated for potential hepatotoxicity (see the “Hepatotoxicity” guideline elsewhere in this table).
Adrenal insufficiency	Grade 2+ (symptomatic)	Hold atezolizumab. Refer patient to endocrinologist. Perform appropriate imaging. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better and patient is stable on replacement therapy (if required) within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 12 weeks.
Amylase and/or lipase increased	Grade 1	Continue atezolizumab. Monitor amylase and lipase prior to dosing.
	Grade 2	Continue atezolizumab. Monitor amylase and lipase weekly. For prolonged elevation (*e.g.*, >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
	Grade 3 or 4	Hold atezolizumab. Refer patient to gastrointestinal (GI) specialist. Monitor amylase and lipase every other day. If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab.
Dermatologic toxicity/rash (*e.g.*, maculopapular or purpura)	Grade 1	Continue atezolizumab. Consider topical steroids and/or other symptomatic therapy (*e.g.*, antihistamines).
	Grade 2	Continue atezolizumab. Consider dermatologist referral. Administer topical corticosteroids. Consider higher potency topical corticosteroids if event does not improve.
	Grade 3	Hold atezolizumab. Refer patient to dermatologist. Administer oral prednisone 10 mg or equivalent. If the event does not improve within 48–72 hours, increase dose to1–2 mg/kg/day or equivalent. Restart atezolizumab if event resolves to Grade 1 or better within 12 weeks. Permanently discontinue atezolizumab if event

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		does not resolve to Grade 1 or better within 12 weeks.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Otherwise, manage as above.
	Persistent and/or severe rash or pruritus, any grade	A dermatologist should evaluate the event. A biopsy should be performed unless contraindicated.
Diarrhea or colitis	Any grade	Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (*e.g.*, increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
	Grade 1	Continue atezolizumab. Initiate symptomatic treatment. Endoscopy is recommended if symptoms persist for >7 days. Monitor closely.
	Grade 2	Hold atezolizumab. Initiate symptomatic treatment. Patient referral to GI specialist is recommended. For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered, after consultation with the trial PI, in patients who are deriving benefit and have fully recovered from the immune-related event.
	Grade 3	Hold atezolizumab.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered, after consultation with the Study Chair, in patients who are deriving benefit and have fully recovered from the immune-related event.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist for evaluation and confirmation biopsy. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
Hepatotoxicity	Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting	Risk of immune-mediated hepatitis. LFTs should be performed immediately, and LFTs should be reviewed before administration of the next dose of study drug. For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should also include pancreatitis, as described below.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
	Grade 1 hepatic event	Continue atezolizumab. Monitor LFTs until values resolve to within normal limits.
	Grade 2 hepatic event, ≤5 days	Continue atezolizumab. Monitor LFTs more frequently until values resolve to baseline values.
	Grade 2 hepatic event, >5 days	Hold atezolizumab. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks.
	Grade 3 or 4 hepatic event	Permanently discontinue atezolizumab. Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
Hyperglycemia	Grade 1 or 2	Continue atezolizumab. Initiate treatment with insulin if needed. Monitor for glucose control.
	Grade 3 or 4	Hold atezolizumab. Initiate treatment with insulin. Monitor for glucose control. Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperthyroidism	Grade 1 (asymptomatic)	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** Continue atezolizumab. Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:**

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		Follow guidelines for symptomatic hyperthyroidism.
	Grade 2+ (symptomatic)	Hold atezolizumab. Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to endocrinologist. Resume atezolizumab when symptoms are controlled and thyroid function is improving. Permanently discontinue atezolizumab for life-threatening immune-related hyperthyroidism.
Hypothyroidism	Grade 1 (asymptomatic)	Continue atezolizumab. Start thyroid-replacement hormone. Monitor TSH weekly.
	Grades 2+ (symptomatic)	Hold atezolizumab. Start thyroid-replacement hormone. Consider referral to an endocrinologist. Monitor TSH weekly. Restart atezolizumab when symptoms are controlled and thyroid function is improving.
Meningo-encepahlitis, immune-related (signs and symptoms in absence of an identified alternate etiology)	All grades	Permanently discontinue atezolizumab. <u>Patient may not resume treatment, regardless of benefit.</u> Refer patient to neurologist. Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
Myasthenia gravis and Guillain-Barré syndrome	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.
Myocarditis	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.
Neuropathy, immune-related (sensory and/or motor)	Grade 1	Continue atezolizumab. Evaluate for alternative etiologies.
	Grade 2	Hold atezolizumab. Evaluate for alternative etiologies. Initiate treatment as per institutional guidelines. Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks.
	Grade 3 or 4	Permanently discontinue atezolizumab. Initiate treatment as per institutional guidelines.
Ocular event (*e.g.*, uveitis, retinal events)	Grade 1	Continue atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a Grade 2 event.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
	Grade 2	Withhold atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks.
	Grade 3 or 4	Permanently discontinue atezolizumab. Refer patient to ophthalmologist. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. For Grade 3 AEs, patient may only resume treatment after consultation with the trial PI; for Grade 4, patient cannot resume treatment, regardless of benefit.
Pancreatitis, immune related	Grade 2 or 3	Hold atezolizumab. Refer patient to GI specialist. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. Patient may only resume treatment after consultation with the trial PI. For recurrent events, permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
Pulmonary toxicity	All pulmonary events	Evaluate thoroughly for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension.
	Grade 1	Continue atezolizumab and monitor closely. Re-evaluate on serial imaging. Consider patient referral to a pulmonary specialist. For recurrent pneumonitis, treat as a Grade 3 or 4 event.
	Grade 2	Hold atezolizumab. Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage (BAL). Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. For recurrent events, treat as a Grade 3 or 4 event.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
	Grade 3 or 4	Hold atezolizumab. Bronchoscopy or BAL is recommended. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. For Grade 3 AEs, patient may only resume treatment after consultation with the Study Chair; for Grade 4, patient cannot resume treatment, regardless of benefit.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. [redacted] at [redacted]) or Dr. [redacted] at [redacted] ([redacted]).

8.5 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 TREATMENT AND SPECIMEN SUBMISSION

REQUIRED STUDIES	Base-line	WEEK																						Off Tx Prior to HG Recur ≠	After HG Recur #
		1	4	7	10	13 *	16	19	22	25*	28	31	34	37	40	43	46	49	61	73	85	97	109+		
PHYSICAL																									
History and Physical Exam	X Σ		x	x	X	x	x	x	x	x	x		x		x		x								
Weight and Perfor-mance Status	X Σ																								
Toxicity Notation Ω		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Ω					X Ω	X Ω
Baseline Abnorma-lities	X																								
Assess pulmonary signs and symptoms α		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Ω					X Ω	X Ω
Disease Assessment ≠						X				X				X				X	X	X	X	X	X q24 wks	X	
LABORA-TORY																									
CMP/ Serum Chemistry €	X λ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
CBC w/ diff, platelets β	X λ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Pregnancy test (if applicable) §	X λ																								
TSH ¥	X λ			x		X		x		X		x		X		x		X							

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REQUIRED STUDIES	Base-line	WEEK																						Off Tx Prior to HG Recur ≠	After HG Recur #
		1	4	7	10	13 *	16	19	22	25*	28	31	34	37	40	43	46	49	61	73	85	97	109+		
PROCE-DURES																									
Bladder Biopsy *ƒ*	X									X															
Cystoscopy ≠	X					X				X				X				X	X	X	X	X	X q24 wks	X	
Urine Cytology ≠ §	X					X				X				X				X	X	X	X	X	X q24 wks	X	
X-RAYS AND SCANS																									
ECG	X																								
CT or MRI	X																			X ¿					
TREATMENT																									
Atezoli-zumab α		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
SPECIMEN SUB-MISSION																									
Slides for Pathology Review (required) Δ	X Θ									X															X
FFPE tissue from TURBT/biopsy π	X									X															X
Whole Blood £	X	X	X	X		X																			
Urine		X				X				X								X		X					
Urine Cytology Slide						X Ψ				X Ψ															

Click here for Footnotes:

Footnotes for 9.1

* If no treatment delays, treatment Cycles 5, 9, 13 and 17 coincide with disease assessment timepoints.
€ Bilirubin, SGOT [AST] or SGPT [ALT], creatinine, glucose, calcium, sodium, potassium, chloride and bicarbonate
β ANC, platelets, hemoglobin
£ Collect whole blood prior to drug infusion. See protocol Section 15.0 for details.
Δ Three H&E stained slides are REQUIRED to be submitted for central pathology review at any time a biopsy is performed for suspected recurrence. See protocol Section 12.0 for details and shipping instructions.
α Atezolizumab is given every 21 days. Vital signs should be monitored before, during, and after infusion. See Section 7.2 for details.
Σ To be performed within two weeks prior to registration
¥ To be performed more frequently if clinically indicated.
≠ Disease assessment will be performed every 3 months (12 weeks) for the first 2 years, then every 6 months (24 weeks) for Years 3-5 until HG recurrence or death. Disease assessment includes office cystoscopy and cytology A biopsy is required for suspicious cystoscopy findings or cytology results positive for malignancy.
Following a HIGH-GRADE recurrence within 5 years after registration, disease assessment is at discretion of treating investigator and the **S1605** Disease Assessment Form does not need to be submitted. However, the **S1605** Follow-up Form is still required for the full 5 year duration or death.
f Bladder biopsy is REQUIRED for patients with any component of CIS at study entry (with or without concomitant Ta/T1 disease) within 7 days of Week 25 after registration, except where noted in Section 7.3. All patients with suspicious cystoscopy findings or cytology positive for malignancy at any of the indicated diseases assessment times (or any other time, i.e. for cause) will undergo biopsy or TURBT. Patient should continue receiving atezolizumab while waiting for biopsy. Submit Pathology report for all biopsies performed, regardless of result.
π Submit FFPE tissue any time a biopsy is performed for suspected recurrence of any type or persistent CIS.
¿ The CT or MRI scan must be performed at Week 73 for all patients who have not had a HG recurrence before that timepoint and scans must be submitted via AG Mednet. See Section 15.2 for instructions.
§ Submit all cytology reports as a RAVE source document.
Ω Follow-up safety assessments are required at 30 days and 90 days after the last dose of atezolizumab, regardless if patient has started a new cancer therapy. Report ALL toxicities, ALL Grades for first 30 days following last dose of protocol treatment on the last S1605 Adverse Event Form. Report ALL toxicities, ≥ Grade 3 for days 31-90 following last dose of protocol treatment on the **S1605** Late Effects Form. Amend original Late Effects form to add any additional toxicities ≥ Grade 3 experienced throughout remaining follow-up period.
Ψ For all patients with CIS at study entry, one urine cytology slide is required for central pathology review. See Section 12.0 for instructions.
Θ Baseline histology used to diagnose disease for eligibility (from biopsy or TURBT), per Section 5.1a.
λ Baseline labs (except TSH) to be obtained within a window of 3 weeks.

Allowable windows

Treatment must begin within 7 calendar days of registration.
Allowable windows for scheduled disease assessments performed every 12 weeks is +/- 14 days, every 24 weeks is +/- 14 days. The window is to be calculated from the scheduled date of the procedure/assessment.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Complete Response

Complete Response: Negative biopsy for high grade disease at Week 25 (± 7 days) for the subset of patients with a CIS component at study entry, according to local pathology call. In addition, patients with a CIS component who undergo negative biopsy at Week 13 for suspicious cystoscopy and or positive cytology and have cystoscopy not suspicious for cancer and cytology not positive for malignant cells at Week 25 do not require repeat biopsy at Week 25 and will be considered to have a complete response at Week 13 and will also be counted as having a complete response at Week 25.

10.2 Complete Response duration

Complete Response Duration: Defined as the time from date of biopsy documenting the complete response to the time of first high-grade recurrence.

10.3 Progression

Progression**:** Biopsy proven muscle invasive bladder cancer Stage ≥ T2, nodal or distant metastasis.

10.4 Event

Event: Histologically proven first appearance of high-grade bladder cancer at Week 13 or later if stage ≥ T1, or Week 25 or later if stage Ta or CIS, muscle-invasive bladder cancer, clinical evidence of metastatic disease, high grade upper tract urothelial carcinoma, high grade urothelial carcinoma of the prostatic urethra, or death due to any cause.

10.5 Recurrence

Recurrence: Histologically proven first appearance of high-grade bladder cancer at Week 13 or later if stage ≥ T1, or Week 25 or later if any stage high-grade, according to local pathology call.

10.6 Progression-Free Survival

Progression-Free Survival: From time of registration to time of first documentation of progression (as defined in Section 10.3) or death due to any cause. Patients last known to be alive and not to have progressed are censored at the date of last contact.

10.7 Event-Free Survival

Event-Free Survival: From date of registration to first documentation of event (see Section 10.4). Patients last known to be alive and not to have recurred are censored at the date of last contact.

10.8 Recurrence-Free Survival

Recurrence-Free Survival: From date of registration to the first documentation of recurrence (as defined in Section 10.5). Patients last known to be alive and not to have recurred are censored at the date of last contact.

10.9 Cancer-Specific Survival

Cancer-Specific Survival: From date of registration to date of death due to bladder cancer. Patients without bladder cancer death are censored at last contact date or date of non-bladder cancer death.

10.10 Overall Survival

Overall Survival**:** From date of registration to date of death due to any cause. Patients last known to be alive are censored at the date of last contact.

10.11 Performance Status

Performance Status: Patients 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.

11.0 STATISTICAL CONSIDERATIONS

11.1 Patient Populations

Eligible patients are defined as registered patients who met all the pre-registration eligibility criteria listed in Section 5 that were in effect at the time of the 12/14/18 amendment. The determination of eligibility regarding Disease Related Criteria will be based on local pathology review.

Evaluable patients are defined as registered patients who received any amount of study drug (atezolizumab).

Efficacy analyses will be based on patients who are determined to be both eligible and evaluable as defined above.

Safety analyses will be based on patients who are determined to be evaluable as defined above. Patients who are registered in the study but who do not receive any study drug will not be included in safety analyses.

11.2 Estimate of Sample Size:

A sample size of 135 eligible patients (evaluable) will be enrolled over 36 months with 18 months of additional follow-up. Our goal is to enroll 70 patients with a CIS component and 65 patients with Ta or T1 disease only. One stratum may be closed prior to accrual completion to ensure adequate patient numbers in both disease groups. An additional 50% will be enrolled to account for ineligibility or initial treatment refusal resulting in a total sample size of 202. With Revision #5 (Version Date 12/14/18) a pre-registration Study Chair approval form was enacted which has significantly reduced the rate of ineligible registrations.

11.3 Analysis:

There will be two co-primary aims for this study: The first objective to be tested involves the complete response rate in the subset of patients with CIS (see Section 10.1). The second co-primary objective involves event-free survival at 18 months for all evaluable patients. A hierarchical approach will be used to test the two co-primary aims. The CIS aim will be tested first. Only if the result is statistically significant will the second primary objective be evaluated. Only patients who received at least one dose of atezolizumab per protocol will be evaluable for these two primary objectives. Both co-primary tests will be conducted at the one-sided 0.05 significance level.

The first primary objective is the estimation of the CR rate in the subset of patients with CIS. Enrollment of 70 eligible and evaluable patients with a CIS component will be ensured. If the total number of patients out of 70 who respond is 28 (40%) or greater, the agent would be considered promising. This design has a significance level (probability of falsely declaring that an agent with a 30% complete response probability is worthy of further investigation) of 4.6%, and a power (probability of correctly declaring than an agent with a complete response rate of 50% is worthy of further investigation) of 96%. Seventy evaluable patients are sufficient to estimate the CR rate at 25 weeks (± 1 week) to within ± 12% (95% confidence interval). Those CIS patients without a biopsy at 25 weeks will be assumed to be non-responders. Duration of CR is defined as the time from date of biopsy documenting the complete response to the time of first high-grade recurrence,and is a key additional secondary endpoint. With a CR rate of 50%, we would expect 35 patients would have a CR. We can estimate the proportion still in CR at 18 months to within ±17% (95% confidence interval).

One interim futility assessment will be made in the CIS subset. We will evaluate the first 25 eligible and evaluable CIS patients for pathologic response at 25 weeks. Since accrual is expected to be slow, accrual will continue while the interim evaluation is underway. A favorable evaluation would be if 7 or more CRs are seen in the first 25 eligible and evaluable CIS patients. This is equivalent to testing the alternative hypothesis of a 50% complete response rate at the one-sided alpha=0.02. If results are favorable, accrual will continue to a total of 70 eligible and evaluable CIS patients.

The second primary endpoint is event-free survival (EFS) (as defined in Section 10.0) at 18 months in the mixed population of patients with either CIS or Ta or T1 disease. This objective will only be tested if the null hypothesis in the first co-primary objective is rejected as specified above. The 18-month EFS estimate will be obtained using the method of Kaplan and Meier, and the Greenwood formula will be used to estimate the variance. A 90% confidence interval will be estimated for the 18-month EFS estimate. If the lower 90% confidence bound excludes 20%, the investigators will conclude the regimen significantly improves EFS relative to historical trial data.

Based on published rates (see table below), it is assumed that if the true 18-month EFS rate in this mixed patient population is ≤ 20%, then this regimen will not warrant further investigation in this setting, whereas a 30% or greater EFS rate at 18 months would be of

considerable interest. This study has a type I error rate (one-sided) of 0.05 and statistical power of 0.93.

There will be one interim analysis conducted at the end of accrual. The 99% confidence interval around the 18 month EFS Kaplan-Meier estimate will be constructed. If the upper confidence bound rules out 30% then consideration will be given to reporting the results early due to futility. There is no adjustment to the alpha for this interim test because it is based on futility. We will not consider reporting early due to efficacy. Because one of the primary endpoints occurs at 18 months and accrual is expected to be steady but modest, an interim analysis of EFS prior to this point in the trial will not be informative.

There are several trials with outcomes that can be used as historical controls for this trial. Most of these are described in Section 2.0.

Drug	Study	Patients	Outcome
Valrubicin	Steinberg 2000	BCG-unresponsive CIS	21% @ 3 mo 17% @ 12 mo 8% @ 24 mo
Valrubicin	Dinney 2013	BCG-unresponsive CIS	10% @ 12 mo 3% @ 24 mo
Gemcitabine	Skinner 2013	mostly BCG unresponsive CIS/Ta/T1 (89% high grade)	28% @ 12 mo 20% @ 24 mo
Gemcitabine	DiLorenzo 2010	mix of BCG failure/unresponsive	19% @ 24 mo
Docetaxel	Lamont 2005	mix of BCG failure/unresponsive	40% @ 12 mo 25% @ 36 mo
MCNA	Morales 2015	mix of BCG failure/unresponsive	20.9% @ 12 mo (FDA analysis)
rAdIFN	Dinney 2015	BCG unresponsive CIS/Ta/T1	35% @ 1 mo

Only Valrubicin is FDA approved in this setting, and is therefore the most representative historic control. Compared to all of these studies, our intended endpoint of 30% EFS at 18 months would demonstrate a clear improvement in outcome.

A secondary aim of interest is the assessment of EFS in the Ta/T1 subset. With n=65 eligible and evaluable patients, there will be 71% power to detect Ho: 20% vs. Ha: 30%, using a one-sided alpha=0.05. Other secondary estimates and confidence intervals of endpoints of progression-free survival (PFS), cystectomy-free survival, bladder cancer specific survival (CSS) and overall survival (OS) will also be provided using Kaplan-Meier estimation. Short-term estimates at 18 months and long-term estimates at 5 years for these secondary endpoints will be of interest. Qualitative and quantitative toxicity assessment will be provided using CTCAE reporting. CR and adverse event rates can be estimated to within ± 9% (95% confidence interval). A toxicity with a true incidence of 1% (5%) has a 69% (99%) chance of being observed at least once in this single arm trial.

11.4 Estimate of Accrual Rate

Target accrual will be 4 patients per month with planned completion of the accrual in 36 months.

11.5 Statistical Plan for Translational Aims

For all analyses in this study, the investigators will consider the use of non-parametric or robust alternatives in the case when distributional assumptions or asymptotic approximations fail. Further, for simplicity, complete follow-up will be assumed on all

patients, but alternative statistical approaches accommodating censoring and potential confounders (e.g. technical batch) will be used if necessary. It will also be assumed that 85% of eligible patients (60 eligible CIS patients and 115 eligible patients in total) will have usable samples for the specified assessment.

Immunohistochemistry (Objective 1.3.b): To assess the association between PD-L1, as quantified via IHC, a dichotomous indicator of positive PD-L1 expression will be created for each patient sample: if ≥ 5% of cells express PD-L1, then the sample will be scored as positive; otherwise, the sample will be negative. Logistic regression will then be used to regress the dichotomous CR status of each CIS patient on the indicator of PD-L1 expression. Fisher's exact test may be used if the proportion of complete responders or proportion of patients expressing PD-L1 is small. Similarly, using all patients, logistic regression will also be used to regress dichotomous 18-month EFS status of each patient on the indicator PD-L1 expression. The analysis will be repeated with CD8 expression as well as other markers. The type I error rate will be controlled at the two-sided alpha=0.05.

For the CR endpoint in CIS patients, assuming baseline CR rate of 30%, then with a sample size of 70, 80% power is anticipated to detect a log odds-ratio of 1.75, 1.59, and 1.52, if the particular marker is positive in 25%, 35%, or 45% of the CIS patients, respectively. For the 18-month EFS endpoint, assuming a baseline 18-month EFS rate of 20%, then with a sample size of 115 patients, investigators anticipate 80% power to detect a log odds-ratio of 1.28, 1.19, and 1.15 if a particular marker is positive in 25%, 35% or 45% of the patients, respectively.

RNA sequencing (Objective 1.3.b): Following preprocessing and normalization of the RNAseq data, it will be determined whether each patient expresses the pre-defined signature. Then to determine whether pre-defined signatures are predictive of complete response in CIS patients, logistic regression will be used to regress CR status for each CIS patient on an indicator for whether each patient expresses the signature. Similarly, to determine whether pre-defined signatures are predictive of 18-month EFS in all patients, logistic regression will be used to regress 18-month EFS status for each patient on an indicator for whether each patient expresses the signature. This analysis will be repeated for each signature considered. Investigators will again consider using Fisher's exact test if the CR or 18-month EFS rates or the proportion of patients expressing the signature are low. Type I error rate will be controlled at the 2-sided alpha=0.05 level.

For the CR endpoint in CIS patients, assuming baseline CR rate of 30%, then with a sample size of 70, 80% power is anticipated to detect a log odds-ratio of 1.75, 1.59, and 1.52, if the percentage of CIS patients expressing the signature is 25%, 35%, or 45%, respectively. For the 18-month EFS endpoint in all patients, assuming a baseline 18-month EFS rate of 20% for patients not expressing the signature, then with 115 patients, investigators anticipate 80% power to detect a log odds-ratio of 1.28, 1.19, and 1.15 if the percentage of patients expressing the signature is 25%, 35% or 45%, respectively.

11.6 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 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 6 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.

Toxicity and accrual monitoring are done routinely by the Study Chair, study statistician, and the Disease Committee Chair. Monthly summary reports on adverse events, SAEs and treatment delays and dose modifications are reviewed by the study chair and study statistician. Accrual reports are generated weekly and formal toxicity reports for a wider

audience are created every 6 months. In addition, SWOG Statistics and Data Management Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicity on an ongoing basis.

12.0 DISCIPLINE REVIEW

12.1 Central Pathology Review

a. All patients registered on this study will undergo central pathology review to confirm diagnosis and determine eligibility. Pathology material must be available for this purpose (see Section 5.0). The review will verify the histologic diagnosis of non-muscle invasive urothelial carcinoma of the bladder and determine the grade and pathologic stage of the tumor. Pathologic review will be conducted on an ongoing basis, but will not be verified prior to patient registration and initiation of study treatment. Similarly, all patients with CIS will undergo central review of urine cytology at 13 and 25 weeks in order to verify complete response. All bladder biopsies taken to evaluate a suspicious lesion in any patient or at the mandatory 25 week time point in patients with CIS will be reviewed centrally, but decisions to continue study treatment will be based on the local pathologist's interpretation.

b. All pathology submissions must be entered and tracked using the SWOG online Specimen Tracking system. See Section 15.1b for information about this system.

c. Pathology materials are to be submitted to the SWOG Biospecimen Bank (Lab #201). The Bank will scan the slides and send to the study pathologist, [redacted], M.D.

All specimens must be shipped at room temperature for overnight delivery, Monday through Thursday (no weekend or holiday deliveries accepted).

d. The following materials are to be submitted for review:

Tissue

1. Three (3) representative diagnostic tumor H & E stained slides.

2. One copy of corresponding surgical pathology report.

Urine Cytology (only patients with CIS component at study entry)

1. 1 urine cytology slide (This should be the routine slide used by the site to do the cytology.)

2. Cytology report

The tissue and cytology specimens used by the study site for diagnosis must be submitted. No special specimen preparation is required. A copy of the Shipment Packing List produced by the 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.

e. Specimens and corresponding reports must be submitted at the following time points:

Tissue

1. Baseline collection, submitted within 7 days after registration. All tissue obtained within 60 days prior to registration for histologic confirmation of recurrent disease (see Section 5.1). For T1 patients, tissue from the prestudy re-resection and original TURBT (even if > 60 days prior to registration) must be submitted.

2. All subsequent biopsies for suspected recurrence including negative biopsies and those that show any recurrence (high or low grade).

3. FOR PATIENTS WITH CIS DISEASE AT STUDY ENTRY: Within 28 days after Week 25 biopsy.

Urine Cytology

1. FOR PATIENTS WITH CIS DISEASE AT STUDY ENTRY: Within 28 days after Week 13 and Week 25 disease assessments.

13.0 REGISTRATION GUIDELINES

NOTE: Prior to registering the first patient, someone at each site must complete the S1605 training by reviewing the PowerPoint presentation located at: https://swog.org/required-S1605-training **and submitting a verification of completion to CTSU by filling in the required fields and clicking "submit".**

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient 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.

a. CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored clinical trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found 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.gov >.

b. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. **IRB Approval:**

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. 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 Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. 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.

2. **Downloading Site Registration Documents:**

Site registration forms may be downloaded from the **S1605** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol **S1605** Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. **Requirements For S1605 Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations, access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
- Verification that at least one site staff member has reviewed the PowerPoint presentation as outlined in Section 13.0.

4. Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal:
www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

Delegation of Task Log (DTL):
Each site must complete a protocol-specific DTL. 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 patients to the study. The DTL application is located on the CTSU members' website at www.ctsu.org. Any individual at the enrolling site on a participating roster may initiate the site DTL. Instructions on completing the DTL are embedded in the DTL.

5. Checking Your Site's Registration Status:

You can verify your site registration status on the members section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients 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** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients 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 abstract page on the SWOG website (www.swog.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. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the RAVE CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. Individuals 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 RSS, 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 users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users 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.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ 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. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

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.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1605 Onstudy Form

S1605 Eligibility Criteria Form
- Fill out electronic version in Rave
- Keep paper version in patient's records at site with registering investigator's signature and date signed

S1605 Pre-Registration Study Chair Approval Form
- PRIOR TO PATIENT REGISTRATION. Please email completed form with any supporting pathology reports to **S1605question@swog.org** at least 5 days prior to planned registration date
- AFTER REGISTERING the patient, please **add the SWOG patient ID** to the top right corner of this form

Upload this completed/signed form as a baseline source document in Rave

Baseline Abnormalities Form

Operative and Pathology Reports (If there is a re-TURBT at baseline, submit both reports from first and second procedure.)

Cytology Report

Baseline Electrocardiogram (ECG) Report

Specimens as outlined in Sections 12.0.

Radiology reports from all scans performed to assess disease.

b. WITHIN 28 DAYS AFTER REGISTRATION:

Submit specimens as outlined in Section 15.0 (if patient has consented).

c. WITHIN 28 DAYS OF DAY 1 OF CYCLES 1, 2, 3, 5, 9, AND 17:

Submit specimens as outlined in Section 15.0 (if patient has consented).

d. WITHIN 7 DAYS AFTER EACH CYCLE OF TREATMENT:

Submit the following:

S1605 Treatment Form

S1605 Adverse Event Form

e. WITHIN 28 DAYS AFTER EACH DISEASE ASSESSMENT UNTIL HIGH-GRADE RECURRENCE, OR MUSCLE INVASIVE DISEASE UP TO 5 YEARS (REGARDLESS OF TREATMENT STATUS):

S1605 Disease Assessment Form

Cytology Report

Pathology Report (if biopsy was performed)

S1605 Follow-Up Form (if patient is off protocol treatment)

f. *FOR PATIENTS WITH CIS DISEASE*, WITHIN 28 DAYS AFTER WEEK 13 AND WEEK 25 DISEASE ASSESSMENT:

Submit specimens and cytology report as outlined in Sections 12.0.

g. BIOPSY FOR SUSPECTED RECURRENCE AT ANY TIME POINT (all patients):

Submit specimens as outlined in Sections 12.0 (Required).

Submit specimens as outlined in Section 15.0 (if patient has consented).

Pathology report

h. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1605 Treatment Form (final)

S1605 Adverse Event Form (final; including ALL toxicities, ALL Grades for first 30 days following last dose of atezolizumab, regardless if patient has started new cancer therapy)

i. 30 DAYS AND 90 DAYS FOLLOWING DISCONTINUATION OF TREATMENT:

S1605 Late Effects Form (all toxicities, Grades ≥ 3 for Days 31-90 following last dose of atezolizumab, regardless if patient has started a new cancer therapy; amend original Late Effects form to add any additional toxicities ≥ Grade 3 experienced throughout remaining follow-up period).

j. FOR PATIENTS WHO HAVE NOT HAD HIGH GRADE RECURRENCE AT 18 MONTHS/WEEK 73 (AT TIME OF CYSTOSCOPIC EVALUATION AND CT/MRI):

Submit specimens as outlined in Section 15.0 (if patient has consented).

Submit images as outlined in Section 15.2 (Required).

Radiology report from the submitted 18 month scan should be uploaded as a source document in Rave.

k. WITHIN 14 DAYS OF HIGH GRADE RECURRENCE:

If on protocol treatment:

Off Treatment Notice

S1605 Treatment Form (final)

S1605 Adverse Event Form (final)

S1605 Disease Assessment Form (final)

Pathology Report

Submit specimens as outlined in Section 15.0 (if patient has consented).

Submit images as outlined in Section 15.2 (Required).

Submit documentation supporting findings of metastatic bladder cancer, muscle-invasive bladder cancer (e.g. pathology report)

If completed/off protocol treatment:

S1605 Disease Assessment Form (final)

Pathology Report

S1605 Follow-Up Form

Submit specimens as outlined in Section 15.0 (if patient has consented).

l. IF CYSTECTOMY IS PERFORMED (bladder removal surgery)

Submit Pathology and Operative Reports from cystectomy procedure (uploaded as source documents in Rave)

m. AFTER HG RECURRENCE, EVERY 6 MONTHS FOR YEARS 1-2, THEN ANNUALLY FOR YEARS 3-5:

S1605 Follow-Up Form

S1605 Late Effects Form (all toxicities, Grades ≥ 3 for Days 31-90 following last dose of atezolizumab, regardless if patient has started a new cancer therapy; amend original Late Effects form to add any additional toxicities ≥ Grade 3 experienced throughout remaining follow-up period)

n. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and **S1605** End of Study Form **and a final S1605** Treatment Summary Form and **S1605** Adverse Event Summary Form (if the patient was still on protocol treatment) or **S1605** Follow-Up Form (if the patient was off protocol treatment) documenting death information.

o. WITHIN 4 WEEKS OF CONSENT WITHDRAWAL, LOST TO FOLLOW-UP OR MAXIMUM FOLLOW-UP OF 5 YEARS:

S1605 End of Study Form

p. PRIOR TO JUNE 1, 2020 (ALL REGISTERED PATIENTS WHO RECEIVED ANY PROTOCOL TREATMENT)

If OFF protocol treatment:

Submit **S1605** Concomitant Medications Form
(*all concomitant medications received while on protocol treatment must be reported*)

If ON protocol treatment:

Submit **S1605** Concomitant Medications Form AND form must be up to date with current concomitant medication data as of June 1, 2020

q. WITHIN 30 DAYS AFTER THE DISTRIBUTION OF REVISION #9 (protocol version date 09/20/2021)

Submit the following:

Baseline TSH & T4 results on the **S1605** Onstudy Form (amend original Onstudy form in Rave)

S1605 Lab Values Form for each cycle of protocol treatment patient received
(if labs were repeated within a treatment cycle, all repeated labs must be reported as well)

Any additional labs or clinical workup done to assess or monitor an adverse event while on protocol treatment (e.g. cultures, EKG, additional labs not listed on the **S1605** Lab Values Form) – describe in the Comments section of the **S1605** Adverse Event Form containing the associated toxicity

r. WITHIN 15 DAYS AFTER SUBMISSION OF ALL DATA REQUESTED IN REVISION #9, RESOLUTION OF ALL QUERIES, AND CONFIRMATION IS RECEIVED FROM THE SWOG STATISTICS AND DATA MANAGEMENT CENTER THAT THE PATIENT'S CHART IS LOCKED IN RAVE

Electronic Signature Page
(*Investigator must check the box and e-sign this page in Rave attesting to the completeness and accuracy of the data, see section 18.5 for more information*)

15.0 SPECIAL INSTRUCTIONS

See Section 12.0 for mandatory central pathology eligibility review submission information.

15.1 Translational Medicine and Banking

Specimens for translational medicine and banking are optional for the patient. The SWOG Specimens Submission webpage for the SWOG Biospecimen Bank – Solid Tissue, (Lab #201), is located at the following URL: https://www.swog.org/member-resources/biospecimen-resources/solid-tissue-specimen-submission.

a. If the patient consents, specimens must be submitted as follows (see Section 9.0):

1. FFPE Tissue from TURBT for IHC, RNA-seq, and Banking

a. FFPE Tissue Specimen Submission Time Points:

i. Baseline –SUBMITTED WITHIN 28 DAYS AFTER REGISTRATION (PRESTUDY TURBT)

Positively Charged Unstained Slides:

Number of Slides	Thickness	Type of Testing
Five (5)	5 mcM	IHC

Sections of Scrolls*:

Number of Scrolls	Thickness	Type of Testing
Four (4)	5 mcM	RNA-seq
Eleven (11)	10 mcM	Banking for future studies **

* NOTE: another term for this type of tissue preparation is “curls”.

** May substitute FFPE block for unstained slides and scrolls. However, 3 H&E stained slides are still required per Section 12.0.

If adequate tissue specimen is not available from TURBT to submit for all of the slides and scrolls listed at any time point above, specimens for RNA-seq will be prioritized over IHC, and these over banking.

ii. AT ANY TIME BIOPSY IS PERFORMED FOR SUSPECTED RECURRENCE AND AT REQUIRED WEEK 25 BIOPSY:

Positively Charged Unstained Slides:

Number of Slides	Thickness	Type of Testing
Five (5)	5 mcM	IHC

Sections of Scrolls:

Number of Scrolls	Thickness	Type of Testing
Four (4)	5 mcM	RNA-seq
Six (6)	5 mcM	Banking for future studies **

** May substitute FFPE block for unstained slides and scrolls. However, 3 H&E stained slides are still required per Section 12.0.

b. FFPE Tissue Specimen Collection and Submission Instructions

SLIDES: For IHC, sites will submit specimens of tumor-containing FFPE tissue as sections on positively charged unstained slides.

SCROLLS: For RNA-seq and banking, sites will section tumor-containing FFPE blocks on site and submit as scrolls in Eppendorf tubes. For banking submission only, sites may submit tumor-containing FFPE blocks instead of scrolls.

Tissue should be sectioned as close to date of shipment as possible **(not more than 2 weeks prior to shipment)**. Sections and scrolls should be stored at 4ºC; batch shipment is allowed.

Tissue blocks can also be submitted, in which case the sites are requested to estimate that enough tissue is submitted to meet the above listed section requirements.

Follow packaging instructions on the SWOG Specimen Submission webpage. Ship to the SWOG Biospecimen Bank – Solid Tissue, (Lab #201).

2. Whole Blood for Banking

a. COLLECTED PRIOR TO TREATMENT START, SUBMIT WITHIN 28 DAYS AFTER REGISTRATION

Collect 5 mL whole blood in one 5 mL sodium-citrate tube. **Note that no additional whole blood processing is required prior to freezing.** Freeze whole blood in sodium-citrate at -80°C until shipment. Whole blood may be batch-shipped on dry ice as long as all specimens are shipped within 3 months of collection.

If this collection is missed prior to treatment start, please collect at next visit.

Follow packaging and shipment instructions on the SWOG Specimen Submission webpage. Ship to the SWOG Biospecimen Bank – Solid Tissue (Lab #201).

b. DAY 1 OF CYCLES 1, 2, 3, AND 5

Prior to atezolizumab administration on these days, collect peripheral blood in lithium heparin-coated vacutainer blood collection tubes. Use the processing worksheet included in the kit provided by the SWOG Biospecimen Bank; required data fields from processing must be entered into SpecTrack to ship

specimens. Immediately transfer 2 mL of the blood to the 15 mL conical tube provided in the kit. Immediately add the Proteomic Stabilizer (PROT1) to the conical tube and mix gently. Incubate for 10 minutes at room temperature and then evenly distribute into labeled, 2 mL cryovials. Store the cryovials at -80°C until shipment. Blood may be batch-shipped on dry ice. Ship within 3 months after collection.

Please refer to instruction sheet included with the specimen kit (Instructions for S1605) for complete Blood Collection and Processing Information.

3. Urine for banking

a. Urine Specimen Submission Time Points

i. DAY 1 OF CYCLES 1, 5, 9, AND 17

ii. AT WEEK 73

b. Urine Specimen Collection and Submission Instructions

Prior to or after atezolizumab administration, collect approximately 30 mL of urine mid-stream in a sterile urine cup.

Aliquot collected urine into 15 mL conical tubes, centrifuge 10 minutes at 1,000g (4ºC), and then freeze (-80ºC) upright until shipment. Urine may be batch-shipped. Ship to the SWOG Biospecimen Bank – Solid Tissue (Lab #201).

b. 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) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Non-SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://crawb.crab.org/SpecTrack/Logon.aspx (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 should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

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

(http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

c. Specimen Collection Kits

S1605 laboratory kits containing the Smart reagent (PROT1) are now available for ordering. The whole blood specimens noted in Section 15.1a.2b. (whole blood collected on Day 1 of Cycles 1, 2, 3 and 5) must be submitted and processed per the instructions provided in the kit.

Note: The Cycle 1 specimen is required for submission of downstream specimens. If a Cycle 1 blood specimen processed with the provided PROT1 buffer has not been submitted, then sites should not submit follow-up whole blood PROT1 specimens.

It is preferred that kits are ordered for registered patients only, because these are uncommon reagents being used for this study and waste should be prevented. If sites can order before noon Eastern, then they should receive the kits 3 – 4 business days after the request, if not sooner.

The kits should be ordered in enough time to receive them prior to baseline collection and can be ordered online at:
https://ricapps.nationwidechildrens.org/KitManagement.

d. TruCulture – All Sites are Eligible to Participate

When you are preparing a patient for registration, please order a TruCulture kit online at https://ricapps.nationwidechildrens.org/KitManagement. Kits will not be provided to sites before an eligible patient is identified.

Upon receipt of the kit, read the instructions included. Maintain the TruCulture syringes at -20 C until time of use.

Prior to atezolizumab administration on Cycle 1 Day 1 and again on Cycle 2 Day 1, collect and process blood as described in the instructions provided in the kit.

15.2 Submission of Images for Banking (Required)

All participants will undergo CT or MRI imaging of the abdomen and pelvis at Week 73 after registration if they have not had a high-grade recurrence. Images must be locally read and interpreted by the local site radiology services. Imaging exams must then be submitted electronically via the AG Mednet service as described below. Specific information about the imaging workflow and instructions can be found at on the **S1605** Desktop Agent application.

a. **Electronic Submission Set-Up**

To request access, email the **S1605** trial administration at:
agmednetadmin@swog.org and provide the following information:
• Contact Name
• Email Address
• Phone Number
• Site Name
• NCI Site Code
• Address
• Trial Name
• Trial ID
• Date

b. **Registration via the AG Mednet Portal**

1. If your site is qualified to participate in the trial, the SWOG Trial Administrator will invite you to the trial via the AG Mednet Portal. When you are added, you will receive a welcome email notification prompting you to register in the portal: https://portal.agmednet.net.

2. Complete the 2 pages of registration information. This includes creating your own username and password and a challenge question and answer.

3. When you are finished with registration, the portal will display a "Registration Complete" page. At this point you now have access to the trial. After you download the Desktop Agent, you will be able to login with your new username and password. You will also receive a registration confirmation email notification.

c. **Download the Desktop Agent and Login**

There are a few basic requirements that must be in place in your computer in order to use the AG Mednet Desktop Agent:

- Computer/Operating System:
  - Windows 7; Windows 8, Windows 10
  - Mac OS X version 10 (rosemite), 10.11 (El Capitan) and above.
- Disk Space/Memory:
  - Sufficient disk space to store temporary local copies of image exams;
  - Minimum of 1 GB of memory.
- Internet Access and Compatible Browser:
  - Internet Explorer Version 11, Mozilla Firefox Version 44, Google Chrome Version 48.x (Windows only),
    Apple Safari version 9.x or newer (Mac only).

- Java 8:
  - You need to have Java 8 installed on your Windows or Mac computer to use AG Mednet.
  - It is likely you already have Java installed. If you do not, you will be prompted to download it after launching the Desktop Agent.
  - We do support the last minor version as well, Java 7 Update 80

- AG Mednet Desktop Agent:
  - For your first upload, visit the AG Mednet Portal: https://portal.agmednet.net. Click on "Launch Desktop Agent."
  - For subsequent uploads, you may launch the Desktop Agent from the AG Mednet Portal, or double-click the "AG Mednet Desktop Agent" icon on your computer desktop.

d. **Submission (DICOM Exam)**

1. Click on the tab "Locate Exam" (top of screen)

2. For CD/DVD, load a disc into your machine

3. A normal directory tree will be visible (close any DICOM viewers that may pop-up). Select the location of your DICOM files (i.e., the CD/DVD drive) or your PACS server. (NOTE: if sending from a PACS or Modality, use the

DICOM Query or DICOM Receive Tab. Further details are available in the user guide on the Welcome Tab)

4. Find the time-point you wish to submit and select the “DICOMDIR” file and click “Import Exam.” Click “Close” when complete*

5. Click the “Exam List” tab (top of screen)

6. Select the exam you want to submit from “Available Exams” by clicking on a row within the table. In the image preview, you will see a picture of the data selected. Please check this is what you intend to submit. If not, select a different exam or go back to step A or E and select a different exam from the exam list.

7. In “Available Tasks for Selected Exam” (bottom left of screen), click “Assign Exam to Trial.” In pop-up box, select **S1605** from drop-down list and click “Assign Trial.”

8. In “Available Tasks for Selected Exam” (bottom left of screen), click “Deidentification” and click “Do Task.”

9. To complete the submission, select “Upload Exam” and then “Do Task.” 10. In the pop-up box, click into the first blank cell under “De-identified Value.” Follow the on screen guidance and enter required data. Then click the next blank cell below the first and repeat until all blank cells are populated. As you complete these cells, the red cross will turn into blue checks. If a red cross remains after data has been entered, please check that the data is correct and change if applicable.

10. In the pop-up box, click into the first blank cell under “De-identified Value.” Follow the on screen guidance and enter required data. Then click the next blank cell below the first and repeat until all blank cells are populated. As you complete these cells, the red cross will turn into blue checks. If a red cross remains after data has been entered, please check that the data is correct and change if applicable.

11. Click out of the cells and click “De-identify” (bottom of pop-up). AG Mednet will then remove any personal patient information from the DICOM metadata fields and replace this information with the study specific data you entered in the table. Click close when complete.

12. In “Available Tasks for Selected Exam” (bottom left of screen), click “Transmittal Form” and click “Do Task.” The Data Transmittal Form will open. Complete all mandatory fields according to the study protocol. If you attempt to save the form without completing all mandatory fields, an alert will appear, prompting you to complete the remaining fields. If you want to print the form, click the “Print” button prior to saving. When the form is complete, click the “Save” button.

13. In “Available Tasks for Selected Exam” (bottom left of screen), click “Upload Exam” and click “Do Task.”

14. Data will now be transmitted. Upload time is variable (depending on network connection and the size and number of images), but AG Mednet can be left running in the background and the computer used for other work. Once the data has been transmitted, a message will pop-up and AG Mednet can be closed.

15. You can import new exams and process them during the upload.

16. After 15 minutes of inactivity, the Desktop Agent will lock out. However, this does not interfere with the upload. You only need to log back in if you want to import another exam.

*In most cases, a DICOMDIR file will be generated by scanners. However, if this is not the case, please select “All Files” from the dropdown box at the bottom of the “DICOM Import” screen. Data can then be selected manually from the directory tree and “Import Exam” clicked. The process is then the same as where a DICOMDIR file exists.

Note: The person responsible for activating the desktop agent should be involved in submitting the exams as the Desktop Agent requires specific log-in verification. All questions regarding AG Mednet use should be directed to 888-9AGMEDNET, and hit 2 for the support option.

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.

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.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator

    (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

   E-mail: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

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.

16.1 Adverse Event Reporting Requirements

a. Purpose

   Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients 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 patient 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 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. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

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 patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is atezolizumab. (**Please note**: The post dosage expedited reporting requirement window has been extended to 90 days rather than the normal 30-day requirement.) If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 90 Days of the Last Administration of the Investigational Agent/Intervention[1] Atezolizumab

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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

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 90 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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a CTEP IND:**

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical source documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center copies of Off Treatment Notice and/or Notice of Death.

2. The following AEs are considered adverse events of special interest (AESI) for this protocol and require expedited reporting via CTEP-AERS. Unless otherwise specified in the list below, events are to be reported regardless of grade or attribution:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism, hypophysitis, and adrenal insufficiency
- Hepatitis
- ALT $>10 \times$ ULN
- AST > 10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, or infusion related reactions
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g. Stevens-Johnson Syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study treatment, as defined below:
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

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

3. 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.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an 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 via CDUS unless otherwise specified.

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

4. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250

San Antonio, Texas 78229

NOTE: If a patient 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 patients 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 patient 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 patient 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 301-230-0159. 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.

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18.0 APPENDIX

18.1 Translational Medicine Studies

18.2 Specimen Banking and Translational Medicine Material Instructions for SWOG Biospecimen Bank (BB)

18.3 Quality Assurance Auditing and Monitoring

18.4 **S1605** Pre-Registration Study Chair Approval Form

18.5 Investigator Electronic Signature

18.1 Translational Medicine Studies

Justification

Checkpoint Blockade

Cancer immunotherapy via immune checkpoint blockade has become an exciting and rapidly evolving treatment paradigm across multiple tumor types, including bladder cancer. Multiple checkpoint molecules have been identified that dampen or inhibit both CD4+ and CD8+ T-cell activation in peripheral tissues. One of these suppressive co-signaling pathways is the programmed death 1 (PD1)/programmed death ligand-1 (PD-L1) axis. Binding of PD-L1 and its relative PD-L2 to the PD1 receptor conveys a state of immune tolerance in the tumor microenvironment. Tumor infiltrating lymphocytes recruited to this environment fail to manifest effector function despite abundance of antigen presentation on antigen presenting cells including tumor cells themselves.

The PD1/PD-L1 axis can be inhibited via monoclonal antibody blockade of either receptor or ligand. High quality clinical evidence is mounting supporting a role of PD1/PD-L1 based therapy. The PD-L1 antibody atezolizumab is an engineered human IgG1 that was approved by the FDA in 2016 as a second line therapy after cisplatin-based chemotherapy in metastatic urothelial carcinoma. The Phase II trial that led to this approval reported on 310 evaluable patients, of whom 45 (15%) demonstrated an objective response, and the response was ongoing at the time of reporting in 38 (84%) of these patients. *(1)*

Markers of Response To Checkpoint Inhibitors

In the Phase I and II studies of patients with metastatic bladder cancer that progressed on cisplatin-based chemotherapy, the immunohistochemical expression of PD-L1 in the tumor-infiltrating immune cells (lymphocytes, macrophages, dendritic cells) but not in the tumor cells was predictive of response to atezolizumab. (2,3) Of the 30 patients with 2-3+ PD-L1 expression in the Phase I trial, 43% experienced an objective response, but only 11% of the other 37 patients with 0-1+ PD-L1 expression responded. Of the 100 patients with 2-3+ PD-L1 expression in the Phase II trial, 26% experienced an objective response, but only 8 and 11% in the patients with 0 and 1+ PD-L1 expression, respectively. Similar findings have been made with other checkpoint inhibitors in metastatic bladder cancer, and across multiple other cancers.

Similar to PD-L1 expression in tumor infiltrating immune cells, simple infiltration by CD8+ cytotoxic T-cells has been shown to predict response to atezolizumab in the Phase II trial. (4) This has been described in other cancers as well. For example, a higher density of CD8+ cells at the invasive tumor margin was observed in melanoma patients responding to pembrolizumab compared to non-responders. (5) This implies that these CD8+ T-cells have been rendered ineffective by the PD-1/PD-L1 axis, but inhibition of this axis disinhibits the cytotoxic T-cells and they are able to exert an anti-tumor effect. Presence of CD4+ cells has not been shown to be predictive, although the subset of FOXP3+ T-regulatory cells have been implicated as markers of chemoresistance in muscle invasive bladder cancer and warrant further investigation. (6) CTLA4 and fractalkine (CX3CL1) are further potential markers that have been reported to have predictive value across different cancers treated with atezolizumab. PD-L2 IHC has not shown a correlation to response to PD-L1 inhibition.

Gene expression signatures derived from whole transcriptome analyses offer the advantage of simultaneous assessment of multiple genes and signaling pathways, with potential for more robust prediction. These signatures incorporate tumor and stromal elements in one marker that does not, for example, allow separation of PD-L1 expression in tumor versus tumor-infiltrating immune cells. Ribas discovered and tested four different immune signatures (“Interferon-gamma 10-gene”, “Expanded-immune 28-gene”, “TCR-signaling” and “Denovo” signatures) in patients with metastatic melanoma receiving pembrolizumab (KEYNOTE-001), and noted correlations to objective response rates and progression-free survival. (7) Likewise, the presence of IFNG and/or IFNA gene expression

signatures identified tumors that were sensitive to immune checkpoint blockade, whereas tumors that contained deletions involving the IFNA locus (and therefore lacked IFN gene signatures) were resistant. *(8)*

Neoantigen burden has been identified as a marker of response to immune-targeting agents. *(9)* The rationale for this is that somatic mutations can result in the exposure of antigenic peptides by the tumor cells to the immune system. Recognition of neoantigens appears to be an important component of cancer immunotherapy. One would therefore expect tumor types with high numbers of mutations to be characterized by strong T cell responses and to be particularly sensitive to immunotherapy. Mutational load correlated to clinical response in non–small cell lung cancer treated with PD-1 blockade and melanoma treated with CTLA4 blockade. *(10,11)* Bladder cancer is known from The Cancer Genome Atlas' (TCGA) pan-cancer analysis to have one of the highest burdens of somatic mutations, which should translate into high neoantigen load. In the phase 2 trial of atezolizumab in patients with metastatic urothelial carcinoma, mutation load correlated with objective response rate and efficiently stratified overall survival. *(12)*.

Building on this same concept, Le et al. reported that deficiency in DNA mismatch repair (MMR) is highly correlated to response to pembrolizumab in colorectal cancer (CRC) and 11 other advanced solid tumors (bladder cancer was not included). *(13)* The objective response rate was 53% (46/86) for all MMR-deficient tumors, and an additional 23% of patients had stable disease. A complete response was observed in 21% of patients. In a previous report in fewer patients, whole-exome sequencing revealed a mean of 1782 somatic mutations per tumor in MMR-deficient tumors, as compared with 73 in MMR-proficient tumors, and high somatic mutation loads were associated with prolonged progression-free survival. *(14)* MMR status is determined by analysis of microsatellite stability. Microsatellites are regions of repetitive DNA where particularly frequent somatic mutations are found when mismatch repair pathways are deficient. The FDA recently approved the use of pembrolizumab for the 2nd line treatment of advanced MMR-deficient solid tumors regardless of tissue of origin.

We hypothesize that vivo inflammatory response to a checkpoint inhibitor may predict response, and we propose to utilize a whole blood syringe-based device called the TruCulture System to test this *a priori*. This system permits us to measure immune responses induced by specific immune stimulants. Myriad Rules Based Medicine (RBM) is a commercial provider of TruCulture tubes. The basic system consists of a single, self-contained syringe, which is preloaded with superantigen (SEB) for T-cell activation. After a fixed interval of incubation, performed at the point-of-care, culture supernatants can be frozen and stored for centralized testing in a CLIA certified laboratory. A broad panel of cytokines can be measured. Genentech has worked with RBM to develop customized tubes that contain atezolizumab alone or in combination with SEB. The hypothesis an enhanced cytokine response after co-stimulation with SEB and atezolizumab will predict favorable treatment response. The appeal of these assay systems for use in personalized immune-oncology is their ease of use, and the ability to implement them at the bedside of patients, thus minimizing technical error introduced by sample collection and manipulation (e.g., ficoll separation, freezing/thawing procedures). Here we propose to test the inflammatory response to atezolizumab in the TruCulture System prior to the first dose of atezolizumab and three weeks after the first dose, and to correlate this to subsequent treatment response. The results of this part of the study could lead to a functional immune assay that could be developed as a companion diagnostic.

Recent efforts have also focused on identification of circulating immune cells for prediction of response to checkpoint blockade. Differences in circulating immune cells, such as an increased abundance of non-classical monocytes and increased absolute lymphocyte counts, have been associated with response to ipilimumab. *(15)* Furthermore, a recent a study by Huang et al., investigated the changes in circulating T cell populations in two cohorts of patients with stage IV melanoma treated with pembrolizumab. The majority (74%) of patients exhibited an immunological response to therapy, identified as an increase

in proliferating (Ki67+) CD8+PD-1+ T cells. The abundance of these cells alone was not predictive of response to therapy. However, when normalized to pre-treatment tumor burden, their abundance during the peak immunological response (3-6 weeks following the start of treatment) was predictive of response to therapy and overall survival. *(16)* Changes in circulating immune cells have also been found to reflect changes in disease states or progression in other cancers. For example, collaborators at the Vancouver Prostate Centre (A. Zoubeidi) have identified PD-L1 positive dendritic cells by flow cytometry in a high proportion of patients with castrate resistant prostate cancer. *(17)*

In this trial we propose to analyze peripheral blood cells as a surrogate marker for altered tumor-associated immune responses to predict response to atezolizumab. We will compare the circulating immune cells with immune-related gene expression patterns of the primary tumor. While tumor immune milieu can only be directly measured at the time of biopsy, peripheral immune cells can be sampled longitudinally at multiple time points by a simple blood draw. This provides additional insight into the dynamics of the tumor immune response before and after therapy with atezolizumab. We will analyze the peripheral immune cells before therapy and at 3, 6 and 12 weeks after starting therapy.

Urine-based genomic test for detection of bladder cancer recurrence

Voided urine offers an abundant supply of cell free and cell associated DNA for genomic analysis. With the advent of affordable next generation sequencing, as well as enhanced understanding of the genomic landscape of urothelial carcinoma of the bladder, it is now feasible to test the genomic profile of urine DNA as a detection marker in non-muscle invasive bladder cancer. Allelic burden of specific mutations, copy number changes and translocations will be monitored to track disease burden. Analysis of cell associated and selected fractions of cell free DNA may also provide a measure of genomic heterogeneity within pre-malignant bladder epithelium and allow monitoring of potential landscaper mutational events and their response to therapy. The non-invasive nature of urine collection permits frequent serial monitoring of genomic response, tumor evolution and disease burden.

We established an assay to identify bladder tumor associated mutations in urine using broad and ultra-deep next generation DNA sequencing of over 100,000 genomic loci (unpublished). Custom sample preservation, molecular biology, and mutation calling software were developed and validated on over 700 reference samples. A bladder cancer diagnostic classifier was then designed using independent clinical cohorts for training (n=34) and test (n=114) on clinical urine samples of both cancer and non-cancer patients. In the validation set, the assay achieved a sensitivity of 93%, specificity of 89%, and incidence adjusted negative predictive value (NPV) of 99.4%. The genomic assay is performed in a CLIA certified laboratory and the algorithm has been locked.

Experimental approach, validated assays employed and expertise of PI:

Immunohistochemistry

IHC for PD-L1 will be performed by Genentech/Roche or in an external commercial laboratory designated by Genentech/Roche using a proprietary antibody (either SP-142 or SP-263) and validated clinical-grade methodology as used in their prior and ongoing clinical trials in bladder and other cancers. (18) Researchers from the Genentech/Roche designated external lab will score the PD-L1 staining intensity using their established scoring system, rating both tumor cells and immune cells as IHC 0, 1, 2, or 3 if < 1%, ≥ 1% but < 5%, ≥ 5% but < 10%, or ≥ 10% of cells are PD-L1 positive, respectively.

IHC will also be performed with anti-CD8 antibody. Image analysis will be used to determine the number of CD8+ cells in specified regions of the tissue, including: i) tumor, ii) invasive front (the boundary between malignant and nonmalignant tissue), and iii) normal

tissue. *(19)* CD8+ lymphocyte density will be calculated in each region using an algorithm described in Cuka et al. *(20)*

Patients with CIS disease will be undergoing bladder biopsy at the 25 week time point. A minority will have residual/recurrent bladder tumor, but normal tissue from the site of the prior tumor will be available from all CIS patients for analysis. At this time point patients will have completed 8 cycles of atezolizumab therapy, and characteristics of the tissue may suggest markers of resistance and response to the drug. IHC will be performed to analyze the same markers. The expression of these markers and the change in their expression over baseline will be correlated with clinical response. The investigators would hypothesize that patients with recurrent/residual tumor will have a lower number of CD8+ cells, as well as a lack of PD-L1 positive immune cells at the 25 week time point. The same analysis will be performed in all patients with biopsies performed for suspected recurrence.

The baseline expression of PD-L1 and CD8 will be correlated with the strain of BCG used prior to entering the trial in an exploratory fashion to determine if BCG strain affects immune marker expression.

RNA Sequencing

RNA-seq will be performed on Illumina's TruSeq RNA Access platform for formalin-fixed, paraffin-embedded tissues by an external laboratory designated by Genentech/Roche, identical to the methods used in the Phase II atezolizumab trial. Analysis will include assignment of all patients to the four TCGA clusters according to the subtyping methods used by the investigators of the Phase II atezolizumab trial. *(21)*

Genentech also has a proprietary signature under investigation that will be tested. (22) Several different previously described multi-gene immune signatures will also be tested in the same RNAseq dataset for their ability to predict response to atezolizumab therapy. (23)

Whole exome sequencing

DNA extraction:
Sections (number and thickness to be defined based on available material) from archived formalin-fixed, paraffin-embedded (FFPE) tissue blocks containing tumour tissues and PBMC will be provided to the VPC. DNA is extracted using a Maxwell RSC instrument (Promega) according to manufacturer's protocols. DNA quality and quantity are analysed using the TapeStation (Agilent Technologies).

Whole exome library preparation:
DNA preparation and enrichment of DNA libraries will follow the Roche SeqCap EZ HyperCap workflow version 2.3. Briefly, DNA is fragmented by sonication (M220 instrument, Covaris) followed by end repair, A-tailing, adapter ligation, clean-up and amplification using the KAPA HyperPrep method (KAPA BioSystems) according to the manufacturer's protocol. After size selection and quantification, pools of DNA libraries (4-plex for tumour DNA and up to 12-plex for germline DNA) are subjected to enrichment by liquid phase hybridization using the SeqCap EZ MedExome probe pool, amplification and clean-up. Quantification and enrichment rate of the captured libraries are performed by qPCR.

Library sequencing:
Pooled libraries are sequenced on an Illumina NextSeq500 sequencing instrument using a paired-end 2x150 bp protocol. The sequencing strategy is to aim for 60x and 200x average sequencing coverage for germline and tumour DNA, respectively.

Sequence read alignment:
Paired-end reads are trimmed to remove adapters, and bases with a quality score <20 are masked. Alignment to the GRCh38.p12 reference genome is performed using BWA-MEM (version 0.7.15) (23); Samtools (version 1.7) (24) is used for sorting and removal of reads with MAPQ<20. Duplicate reads are marked and removed with Picard (version 2.18.0) (http://broadinstitute.github.io/picard/). Base level statistics, including depth and nucleotide counts, are generated using Pysamstats (https://github.com/alimanfoo/pysamstats).

Identification and characterization of mutations:
A version of the following method will be used where variant filtering is adjusted based on observed sequencing depth. Somatic single nucleotide variants (SNVs) and insertion/deletions (indels) are called when their variant allele frequency (VAF) was above 2% with at least 10 supporting unique reads in locations with above 30× depth. Candidate mutations are discarded if the VAF is less than 3× that of the paired WBC or less than 20× the background error rate, defined as the mean VAF of the substituted base(s) across all WBC controls at the corresponding position(s). For variants adjacent to genomic repeats or regions with a strongly predominant base (>80% of local bases), we required a VAF >40× the background error rate. Variants are also filtered if their mean distance from the end of supporting reads was <6 bases. Functional annotation is performed using Annovar (25), and SNVs and indels identified in the Exome Aggregation Consortium (ExAC) database with population allele frequencies >5% are discarded. Most relevant final variants are manually verified in Integrative Genomics Viewer (IGV) 2.3.90 (26).

Optional: putative germline variants are identified from WBC data and defined as non-reference bases with VAFs between 30% and 70% and a minimum read depth of 40×. The pathogenicity of non-truncating missense variants was assessed using ClinVar annotation of clinical significance and/or the availability of COSMIC IDs.

<u>TruCulture</u>

The TruCultue analysis will be conducted only at designated trial sites. Only 50 patients will be analyzed on the trial. These sites will be contacted individually to request participation.

We will use the TruCulture system for measurement of systemic immune response before and after treatment with atezolizumab. TruCulture has been developed by Myriad-Rules Based Medicine as a point-of-care whole blood syringe-based assay for the measurement of multiple cytokines in peripheral blood. We propose to use five different tubes for each patient assay: 1) 1 tube containing SEB for baseline systemic response; 2) 1 tube containing SEB and atezolizumab to test ability of atezolizumab to enhance the systemic response; 3) 1 tube with atezolizumab alone as a control; 4) 1 tube with BCG to test response after prior intravesical therapy; and 5) a null tube for negative control. The syringe, which is designed for integrated collection and culture, is pre-loaded with 2 mL of buffered media containing the selected stimulant (e.g. SEB) which can trigger a T-cell response (expansion/activation) and resultant cytokine production. We will test whether the comparison of cytokine response in the presence and absence of atezolizumab prior to therapy can predict response to atezolizumab.

TruCulture syringes will be sent to participating sites and maintained at -20°C until time of use. Before use the TruCulture tubes will be removed from the freezer and allowed to warm up to ambient temperature. Blood will be obtained from the antecubital vein with the syringe systems fitting directly into a vacutainer set. Exactly 1 mL will be drawn into each of the five TruCulture syringes. Within 15 minutes, the tubes will be inserted into a dry block incubator and maintained at 37°C for 48 hr. At the end of the incubation period, the tubes will be opened and a valve inserted, stopping the stimulation and partitioning the liquid supernatant. The tubes will be re-capped and immediately frozen at -80°C until testing. Sampling time points will include prior to the first dose of atezolizumab and prior to the

second dose of atezolizumab. In each case the blood will be drawn on the day of drug administration.

Centralized analysis will be performed using Luminex xMAP technology in a CLIA-certified third party laboratory designated by Roche/Genentech. For whole blood stimulation, we will utilize the eighteen cytokines that have been previously defined as the core BCG signature. The Least Detectable Dose (LDD) for each assay will be derived by averaging the values obtained from 200 runs using the matrix diluent, and adding 3 standard deviations to the mean. The Lower Limit of Quantification (LLOQ) will be determined based on the standard curve for each assay.

Mass Cytometry

Peripheral blood will be collected in lithium heparin-coated vacutainer blood collection tubes. Proteomic Stabilizer 1 buffer (Smart Tube Inc) will be added to 2 ml blood in a 5 ml cryovial as soon as possible (within 30 minutes). After 10 minute incubation at room temperature, the blood will be frozen to -80°C and shipped on dry ice for central analysis by cytometry by time of flight (CyTOF). Blood will be drawn before the 1st, 2nd, 3rd and 5th doses (on day of atezolizumab administration).

Samples will be thawed and red blood cells will be lysed using Smart Tube's lysis buffer according to the manufacturer's instructions. Samples will then be barcoded with a combination of palladium isotopes using Fluidigm's barcoding kit, and up to 20 samples will be pooled and stained together using Fluidigm's standard protocols. Barcoding prevents variation in staining intensity between different samples due to technical variation.

Cells will be incubated with Fc block to prevent non-specific antibody binding by Fc receptors, and will be stained with a panel of surface markers. The cells will then be permeabilized and stained with a panel of antibodies specific intracellular proteins such as Ki67. Data will be acquired on a CyTOF2 machine (Fluidigm) at the BC Cancer Research Centre (affiliated with the Vancouver Prostate Centre). The staining panel will contain antibodies specific for a broad range of immune cells including, CD4+ and CD8+ T cells, B cells, dendritic cells (DC), monocytes, myeloid derived suppressor cells, natural killer (NK) cells, and granulocytes. The staining panel will also include markers for deeper phenotyping of immune cells including, markers of T cell and antigen presenting cell activation and subtypes, and a panel immune checkpoints and their ligands.

Genomic analysis of urine

Total nucleic acid will be isolated from voided urine (30 mL) with the QIAmp total nucleic acid isolation kit. Nucleic acid will be sequencing adapter ligated and enriched for 90 of the most recurrently altered bladder cancer genes including mutations, CNV and translocations. Next generation sequencing will be performed on Illumina NextSeq or HiSeq instruments. Targeted enrichment of a focused panel of recurrently altered bladder cancer genes will permit very deep (>10,000x depth) sequencing allowing detection of genomic abnormalities as low as 0.1% abundance. Bioinformatic analysis will be conducted using custom designed pipeline which integrates noise suppression algorithms to aid in high confidence identification of mutations, copy number variation and translocations. Through serial urine collection and analysis we can also compare allelic burdens over time within individual patients.

Data analysis performed by:

1. [redacted]Ph.D., SWOG, will lead all data analysis.
2. The biomarker team at Genentech/Roche designated external lab will assist with IHC analysis (lead: [redacted]Ph.D./[redacted], Ph.D.).

3. Bioinformatic assistance with RNA-seq, WES, and TruCulture analysis will be provided by Genentech/Roche (lead: [redacted], Ph.D./[redacted], Ph.D.)
4. Analysis of the data related to peripheral immune cells will occur at the Vancouver Prostate Centre under the direction of [redacted], MD.
5. Analysis of data related to cell free DNA in urine will be performed by Convergent Genomics under the direction of [redacted], MD and [redacted], Ph.D.

Who will be performing testing?

1. PD-L1and CD8 immunohistochemistry – Genentech/Roche or in an external commercial laboratory designated by Genentech/Roche
[redacted], PhD or designate
Corporate Headquarters
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

2. RNA-seq analysis – Genentech/Roche or in an external commercial laboratory designated by Genentech/Roche
[redacted], PhD or designate
Corporate Headquarters
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

3. Whole exome sequencing (neoantigen load) – Genentech/Roche or in an external commercial laboratory designated by Genentech/Roche
[redacted], M.D. or the Vancouver Prostate Centre
Corporate Headquarters
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

4. TruCulture analysis - Genentech/Roche or in an external commercial laboratory designated by Genentech/Roche
[redacted], PhD or designate
Corporate Headquarters
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

5. Mass Cytometry – [redacted]
Vancouver Prostate Centre
2660 Oak St,
Vancouver, BC
V6H 3Z6

6. Analysis of cell free DNA in urine - [redacted]
Convergent Genomics
499 Illinois St. Suite 210
San Francisco, CA 94158

18.1 References

1 Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 387: 1909-1920, 2016.

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18.2 Specimen Banking and Translational Medicine Material Instructions for SWOG Biospecimen Bank (BB)

The Bank will provide kits for collection of blood for mass cytometry to sites via the Kit Management Application. The kits will include the Proteomic Stabilizer 1 buffer (Smart Tube Inc) in a 5 ml cryovial. Sites will provide all other collection and processing supplies.

The Bank will receive FFPE tissue specimens (slides and scrolls or block); frozen whole blood collected in sodium citrate, frozen whole blood processed with Proteomic Stabilizer 1 buffer (PROT1) for mass cytometry, frozen whole blood collected in TruCulture tubes, and frozen urine.

Upon receipt, the Bank will accession, barcode, and store the FFPE tissue scrolls/slides/blocks at room temperature. H&E slides received for central pathology eligibility review will be scanned to a virtual image and sent to Dr. [redacted] via the Virtual Imaging for Pathology, Education & Research (VIPER) application system.

The SWOG Statistics and Data Management Center will provide a list of cases and number of slides that the Bank will prepare to distribute in batches throughout the study to [redacted] (or designee) at Genentech for PD-L1 and CD8 immunohistochemistry staining, as well as RNAseq analysis.

[redacted], Ph.D.
Corporate Headquarters
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

Upon receipt, the Bank will accession, barcode, and store the 5 mL frozen blood in sodium citrate tubes in a -80°C freezer. The bank will send these samples to Vancouver at the end of the study.

Upon receipt, the Bank will accession, barcode, and store the TruCulture tubes in a -80°C freezer. The bank will send these to Genentech once 50 patient samples have been collected.

Upon receipt, the Bank will accession, barcode, and store the 5 mL cryovials of blood in PROT1 buffer for mass cytometry in a -80°C freezer. The bank will send these samples to Vancouver at the end of the study.

Upon receipt, the Bank will accession, barcode, and store the frozen urine in a -80°C freezer. The bank will send these samples to Convergent Genomics at the end of the study.

18.3 Quality Assurance Auditing and Monitoring

The Quality Assurance Program of the Groups participating in the NCTN was developed to enhance the reliability and validity of clinical trials data through the use of routine monitoring procedures which includes auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the SWOG Statistics and Data Management Data Operations Center and to verify compliance with protocol and regulatory requirements. The program also surveys data management practices at each institution in order to provide educational support to the sites regarding issues related to data quality, data management, and other aspects of quality assurance.

Audits are conducted according to FDA regulations and NCI guidelines for Auditing Clinical Trials for the National Clinical Trials Network (NCTN) Program, NCI Community Oncology Research Program (NCORP) and Research Bases:
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmbauditguidelines.pdf.

Each institution is audited at least once every three years, but remains at annual risk of an audit. Routine monitoring of Institutional Performance Review reports and timeliness of reporting of Serious Adverse Events is conducted to identify institutions that may require more frequent audits.

The audit team consists of qualified individuals capable of providing a medical assessment of the patient cases (Quality Assurance staff, physician, nurse or experienced clinical research associate [CRA]). A number of patients equal to 10% of the accrual since the last audit with a minimum of three are randomly selected for review at each institution. In addition, a limited review of eligibility and consent only is conducted for at least one unannounced case at each on site audit.

The major objective of the audit process is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data against the source documents. Primary source documentation reviewed during an audit includes the following: research records, hospital charts, clinic charts, lab reports, x-rays, scans, radiotherapy reports, operative reports, pathology reports and other special studies required by protocol.

By comparing the data collection forms submitted to the SWOG Statistics and Data Management Center with the primary records and referring to the protocol, the audit team reviews the records to determine compliance with protocol requirements for eligibility, treatment administration, response assessment, toxicity reporting and general data quality. Auditors verify that the current IRB-approved version of the consent form was signed prior to registration and that subjects were informed of new findings that could affect their willingness to participate in the study. NCTN investigators and institutions are expected to follow the protocol and lead Group policies in treating patients registered on Group protocols. Among other requirements, investigators/institutions must follow SWOG's policies for dosing principles, reporting of Serious Adverse Events, and follow-up of all patients.

The audit team also verifies that the protocol and its amendments received initial and continuing IRB review and approval and that safety reports and serious adverse events were submitted to the IRB. Investigational drug accountability record forms (DARFs) are reviewed and random patients are cross referenced against the medical record. A tour of the pharmacy is conducted to verify security and storage conditions as well as the physical inventory.

The audit report is comprised of three components: 1) conformance to IRB and informed consent requirements, 2) the pharmacy and use of NCI DARFs, and 3) patient case review. An acceptable rating requires no deficiencies, few lesser deficiencies, or major deficiencies that were addressed prior to the audit. Institutions found to be "unacceptable" or

"acceptable, but requires “follow-up” on any component are required to submit a written response and/or corrective and preventative (CAPA) action plan. Failure to submit a written response including a corrective and preventative action plan within the required timeframe will result in suspension of registration privileges. A re-audit of any component rated as unacceptable will be conducted within one year after the unacceptable audit. An unacceptable rating for the same audit component on two consecutive audits will result in probation. Accrual will be suspended pending submission of a site improvement plan that addresses key infrastructural issues contributing to poor performance. An unacceptable rating at the second re-audit may result in termination from the group. If systematic misrepresentation of data is identified, an immediate repeat audit is scheduled by the representatives from the Group with the NCI and/or the FDA present.

In some cases, non-compliance for issues such as timeliness of data submission, SAE reporting and submission of specimens is monitored off site rather than scheduling a re-audit. Failure to show improvement may result in scheduling of a re-audit or other disciplinary action.

Results of all Quality Assurance Audits are entered into the CTMB-AIS database and reported to the NCI, the Principal Investigator of the institution that was audited, and group leadership. Protocol specific audit results are also sent to the Statistics and Data Management Center to inform the statisticians, data chairs and study chairs of any significant discrepancies involving eligibility, treatment, toxicity or response assessment.

The Quality Assurance Program performs their educational role through several mechanisms including presentations during the Group Meetings, online Clinical Trials Training Courses, collaboration with others such as the Pharmacy Committee and Statistics and Data Management Center to develop training tools, and memos and newsletter articles that are distributed to all Group institutions to educate research staff about changes in regulatory and quality assurance issues and audit procedures.

Additional Monitoring

In addition to the standard auditing process outlined above, the following additional requirements will be implemented for this study:

- Routine monitoring by Data Coordinators at the Statistics and Data Management Center.
- Risk-based monitoring by Monitors at the Statistics and Data Management Center.
- Additional on-site monitoring visits by Quality Assurance Auditors at the Operations Office.

a. Routine Monitoring at the SWOG Statistics and Data Management Center

Data Coordinators at the SWOG Statistics and Data Management Center (SDMC) will perform routine monitoring with the following actions:

Monitor data quality through routine review of submitted data such as on-study, baseline and follow up tumor assessment, lab, treatment, off treatment, and follow up case report forms to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site.

Analyze site characteristics, performance metrics and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance through the SWOG Institutional Performance Reporting mechanism and other available reports.

- Verify critical source data remotely via the collection and review of pathology, radiology and applicable lab reports. This includes the review and confirmation of appropriate disease classification as determined by the pathology report, and assessment of response to treatment based on scan reports uploaded to the Electronic Data Capture (EDC) system and submitted follow-up disease assessment forms.
- To assure data are as consistent, complete and accurate as possible, all subject data must undergo careful review by Data Coordinators (DCs). After verifying that all data forms required to determine eligibility have been received or at a time point designated when all the required forms should have been received, the DC reviews the data and completes an initial evaluation.

The initial review includes the following:

- Determine that all required data fields on each form were completed and are consistent with other data.
- Determine if all prestudy tests and exams were performed within protocol specified time limits.
- Determine if each eligibility criterion was met and properly documented.
- Review and confirm pathology based on the pathology report uploaded to the EDC system.
- Verify that stratification and/or descriptive factors (if applicable) were correctly identified at registration.
- Verify that the subject received the assigned study treatment and correct dose(s).
- Verify that the treatment was started within the time limit indicated in the protocol (if applicable).
- Determine if adverse events reported are consistent with other data and entered as required by study specifications.
- Post internal notes to add additional information which may be useful to the study sponsor, monitors, or statisticians, but which do not require action by site personnel.
- Use the query tool to request additional data classifications and corrections of the CRA.

The DC will perform subsequent review of data when new data become available or queries are answered. Regular review will also occur while patients are still on-study, at the time of progression, once they are removed from study and at the time of death.

Subsequent reviews include the following:

- Determine if all required data fields on each newly submitted form were completed and consistent with other data.
- Evaluate all new treatment documentation for correct treatment and dose.
- Conduct assessment of response to treatment based on scan reports uploaded to the EDC and submitted disease assessment forms.
- Review and code any new concomitant medications as required by study specifications.
- Evaluate if the subject is or should be off protocol treatment per protocol criteria.
- Review and evaluate death if death of subject is reported.
- Use the query tool to request additional data classifications and corrections.

- Post internal query notes to add additional information that may be useful to the study sponsor, monitor, or statisticians but which do not require action by site personnel.
- Review site responses to the queries and the corrected or amended eCRF pages. When corrections and responses are considered satisfactory, queries are closed by the data coordinators. Unsatisfactory responses are re-queried and tracked.
- Perform re-evaluations promptly after responses to queries are received.

b. Centralized Risk-based Monitoring at the Statistics and Data Management Center (SDMC)

Monitors at the Statistics and Data Management Center (SDMC) will support the risk based monitoring approach for this trial with the following actions:

Off-site monitoring to include auditable elements through administration of the second course of treatment and Weeks 13 and 25 disease assessment for the first two patients registered at each site where an onsite audit has not yet occurred.

For instructions for uploading documents in the SDP see protocol section 18.3d.
Documents required:

- Eligibility: Informed Consent title page, signature page and responses to Future Contact and Samples for Future Research Studies, S1605 Eligibility Criteria form, , source documents to support the following: Onstudy labs, H&P, baseline AEs, ECG, Baseline Prior Treatment form

- Cycle 1: AE/SAE, and treatment records, source document for pulmonary signs and symptoms

- Cycle 2: Week 7 labs, AE/SAE, treatment records, source document for pulmonary signs and symptoms

Please note:

- The **S1605** Registration Worksheet and **S1605** Eligibility Criteria form must be signed and dated by the PI
- Baseline Onstudy labs must be within 42 days prior to Registration
- Treatment records must include physician orders and administration records/logs including reasons for dose modifications

c. Onsite Monitoring

- Additional on-site monitoring visits with the first site visit within 6 months of first
- patient registration.
- Monitoring visits will be combined with other routine audits whenever possible. The initial monitoring visit may be postponed up to 3 months to coincide with a routine audit or to coincide with a routine audit of another institution in the same geographic area. Monitoring visits may also be postponed if no accrual or activity has occurred beyond the timeframe covered by the off-site central monitoring.
- Subsequent monitoring visits will be conducted according the following criteria:
- If > 5 patients per year (~ 10% of sites) – annually
- < 5 patients per year – semiannually

- More frequent monitoring visits to a site may be scheduled in response to several factors – high rate of accrual, unacceptable monitoring visit results, centralized electronic monitoring outcome, turnover in staff, etc.
- All sites that receive and dispense investigational agents must be monitored on site to allow at least one visit to the pharmacy with the following exceptions:
    - Sites that use a centralized pharmacy may be monitored at this central location.
    - After an initial onsite visit, NCORP sites and LAPS/Main Member Affiliates may be monitored at a central location.
    - Pharmacies monitored during SWOG site visits for other studies will suffice for the onsite monitoring requirement.
    - The need for subsequent onsite visits will be determined on a case by case basis including past audit results, number of patients on the investigational agent, etc.

Communication of Monitoring Results

The monitoring team will meet routinely to share all aspects of monitoring (on site, centralized, safety, for-cause). When needed, the SWOG Executive Officer for Quality Assurance will be consulted.

All monitoring visits results will be reported according to NCI-CTMB requirements via the CTMB-AIS data base and regularly reviewed by SWOG monitoring staff.

Summarized results of all monitoring visits will be provided semi-annually to the SWOG Board of Governors and the study team. Any problems or issues of concern will be reported to the Data and Safety Monitoring Committee on an as-needed basis.

Safety Specific Centralized Monitoring at the Operations Office

Each Serious Adverse Event (SAE) report submitted (via CTEP-AERS) will be reviewed by the SWOG SAE Coordinator. Supporting documentation for any deaths on study will be requested and compiled with the report and sent to the Physician Reviewer. As mentioned below all sites will undergo mandatory training and this will include training regarding SAE reporting. SWOG regularly monitors timeliness of SAE reporting and addresses any issues of poor performance with individual sites.

The study will be monitored for under reporting/missed Serious Adverse Events: The SWOG SAE Coordinator receives a weekly report from the data base that includes all adverse events that are submitted through routine submission that potentially also meet expedited reporting criteria but for which no CTEP-AERS report is found. The Coordinator is responsible for following up with the responsible site to ensure that SAEs are not missed/under-reported.

The study will be monitored for trends in Serious Adverse Events: A “new SAE on study” report is generated each time a new Serious Adverse Event is entered into the SWOG data base. It is a cumulative report that lists all SAEs reported for the protocol. This allows those who review the report to identify concerning trends in reported events; events that may be occurring at greater intensity (higher toxicity grade) or frequency than expected. The SAE Coordinator, Physician Reviewer, Study Chair, and assigned Statisticians are responsible for regularly monitoring this repo

Additional Approaches to be Used

- Mandatory training of key site personnel prior to first patient registration.
- Timely review of all monitoring reports to identify sites that require additional training, monitoring, disciplinary action, etc.
- Mentoring visits and additional communication between monitor and site staff to assess potential problem areas, provide feedback on data submission quality and timeliness, identify staff turnover, etc.
- Additional mandatory centralized training to be provided to all sites if major changes to the protocol occur or common problem areas are identified.

Management of Noncompliance

Issues of particular concern related to patient safety and questions of site fraud will be managed according to SWOG standard policies and the policies of the NCI CTMB for auditing of clinical trials under the NCI National Clinical Trials Network (NCTN) Program.

Where important deviations are discovered, additional site training components will be developed and implemented.

As with standard NCTN procedures, sites will be required to develop and implement corrective action plans in response to any deficiencies identified at a monitoring visit.

Ensuring Quality Monitoring

All staff involved in monitoring are required to undergo training in the principles of clinical investigations and human subjects protection. They are also required to complete the same protocol specific training required of the site staff.

All monitoring and auditing processes for the study will be reviewed by study leadership twice per year to ensure conformance to the monitoring plan.

Monitoring Plan Amendments

At each formal review of the monitoring plan and conformance to it, the study leadership will make a recommendation regarding the need for amendments to the monitoring plan. These amendments will be reviewed and approved by the NCI and provided in this protocol section and will be submitted to the FDA.

d. Instructions for Uploading Source Documents for the Off Site Centralized Monitoring Review by Statistics and Data Management Center (SDMC) Monitors

Per protocol Section 18.3, a source document review is to be conducted by SDMC monitors for the first 2 patients registered to treatment at each study site where an onsite audit has not yet occurred. The SDMC monitor will notify the head CRA within 5 weeks of registration of the upcoming review. This will allow ample time to begin uploading source documents through the first two courses of treatment and first two disease assessment timepoints. All source documents will be uploaded to the **Source Document Portal (SDP)** which can be accessed directly through CTSU.org by going to the Auditing and Monitoring tab and selecting Source Document Portal. The SDP can also be accessed through Medidata Rave.

Sites will use the SDP to upload source documents to confirm eligibility and activities for Cycles 1 and 2 and for the Weeks 13 and 25 Disease Assessments.

Documents required:

- Eligibility: Informed Consent title page, signature page and responses to Future Contact and Samples for Future Research Studies. S1605 Eligibility Criteria form and S1605 Registration Worksheet must be signed by the Registering Investigator, source documents so support the Onstudy labs, H&P, source document for baseline AEs, ECG, and source documents to support Baseline Prior Treatment form
- Cycle 1: AE/SAE, and treatment records, source document for pulmonary signs and symptoms
- Cycle 2: Week 7 labs, AE/SAE, treatment records, source document for pulmonary signs and symptoms

Please note:

- The **S1605** Eligibility Criteria form and S1605 Registration Worksheet must be signed and dated by the Registering Investigator
- Baseline Onstudy labs must be within 42 days prior to Registration
- Treatment records must include physician orders and administration records/logs including reasons for dose modifications

The SDP in CTSU provides a tool to redact PHI. Please ensure all source documents are properly and completely redacted and free of PHI.

CTSU recommends that users complete the training “CTSU Central Monitoring Using the Source Document Portal (SDP)” which is posted on the CTSU website under Resources -> Educational Multimedia -> Webinars.

For questions regarding the SDMC monitoring please contact centralmonitorquestion@crab.org

18.4 **S1605** Pre-Registration Study Chair Approval Form

SWOG
S1605 PRE-REGISTRATION STUDY CHAIR APPROVAL FORM

Patient Identifier ☐☐☐☐☐☐ **Study Identifier** S 1 6 0 5 **Registration Step** ☐

Patient Initials _____ (L, F M) **Sex:** ☐Male ☐Female

Instructions: This form must be completed by the registering institution and signed by one of the S1605 study chairs PRIOR TO PATIENT REGISTRATION. Please email completed form with any supporting pathology reports to **S1605question@swog.org** at least 5 days prior to planned registration date. Register patient within 30 days of study chair's signature date. After registering the patient, please **add the SWOG patient ID** to the top left corner of this form.

- Keep paper copy of this completed/signed form in the patient's binder at the site
- Upload this completed/signed form as a baseline source document in Rave

Disease Related Criteria *(sections 5.2a- 5.2g)*

Check all that apply and please include any/all supporting path report(s): ☐CIS ☐Ta ☐T1

Date of most recent TURBT: ☐☐ / ☐☐ / ☐☐☐☐ *(If T1 disease, this should be the date of the re-TURBT per section 5.2f)*

If patient has T1 disease, date of prior T1 High-grade diagnostic TURBT/biopsy:
☐☐ / ☐☐ / ☐☐☐☐

Date of most recent cystoscopy: ☐☐ / ☐☐ / ☐☐☐☐

Date of most recent urine cytology: ☐☐ / ☐☐ / ☐☐☐☐

Results of cytology positive for malignant cells? ☐Yes ☐No

If male patient with Ta/T1 disease (but absence of CIS) and cytology positive for malignant cells,

Date of biopsy of the prostatic urethra: ☐☐ / ☐☐ / ☐☐☐☐

Date of most recent CT or MRI (including CT-IVP, CT-urogram or MR-urogram) of the abdomen and pelvis to rule out upper tract malignancy and intra-abdominal metastases: ☐☐ / ☐☐ / ☐☐☐☐

Prior BCG Therapy *(section 5.3a)*

List dates of all prior BCG instillations, beginning with the most recent:

#	Date of Instillation	#	Date of Instillation	#	Date of Instillation
1	☐☐ / ☐☐ / ☐☐☐☐	8	☐☐ / ☐☐ / ☐☐☐☐	15	☐☐ / ☐☐ / ☐☐☐☐
2	☐☐ / ☐☐ / ☐☐☐☐	9	☐☐ / ☐☐ / ☐☐☐☐	16	☐☐ / ☐☐ / ☐☐☐☐
3	☐☐ / ☐☐ / ☐☐☐☐	10	☐☐ / ☐☐ / ☐☐☐☐	17	☐☐ / ☐☐ / ☐☐☐☐
4	☐☐ / ☐☐ / ☐☐☐☐	11	☐☐ / ☐☐ / ☐☐☐☐	18	☐☐ / ☐☐ / ☐☐☐☐
5	☐☐ / ☐☐ / ☐☐☐☐	12	☐☐ / ☐☐ / ☐☐☐☐	19	☐☐ / ☐☐ / ☐☐☐☐
6	☐☐ / ☐☐ / ☐☐☐☐	13	☐☐ / ☐☐ / ☐☐☐☐	20	☐☐ / ☐☐ / ☐☐☐☐
7	☐☐ / ☐☐ / ☐☐☐☐	14	☐☐ / ☐☐ / ☐☐☐☐		

Did patient achieve a disease-free state after receiving BCG (low-grade tumor is considered disease free)?
☐Yes ☐No

If Yes, Date of last high grade tumor TURBT/biopsy prior to starting BCG: ☐☐ / ☐☐ / ☐☐☐☐

(continued on next page)

SWOG
S1605 PRE-REGISTRATION STUDY CHAIR APPROVAL FORM

Patient Identifier | | | | | | | **Study Identifier** | S | 1 | 6 | 0 | 5 | **Registration Step** | |

Patient Initials _____ (L, F M)

S1605 STUDY CHAIR ONLY

Based on the information provided, this patient appears to meet S1605 eligibility criteria 5.2a-5.2g and 5.3a. If the information provided is accurate/complete and patient meets all other eligibility criteria specified in section 5.0 of the protocol, this patient should continue to registration on S1605.

Study Chair Signature: _____ Date: _____

Dr. Peter Black/Dr. Parminder Singh

Comments

18.5 Investigator Electronic Signature

S1605 requires an investigator to sign off on the data for each patient. This will be done within Rave using an electronic signature. The treating investigator may sign off on their own patient(s), or the site PI may sign for all **S1605** patients at their site. The person who signs will be held responsible for the accuracy and completeness of ALL submitted data.

Note: The investigator must be assigned to the Rave Investigator task on the site Delegation of Task Log (DTL) prior to completing the e-signature(s). If they are not assigned on the DTL, they will not have Rave access to this study. If you have questions about the DTL or the signing process, please contact gu@crab.org.

Investigator Instructions for Completing the e-Signature in iMedidata

When you first login to iMedidata, there will be a list of studies that you have been given access to in the middle of the page. Use the search bar to find "**S1605**" and select the link for "Rave EDC":

The signature should be done using the "Site Investigator" role. If you have more than one role on your account, be sure to select "Site Investigator" from the Role Selection drop down when you log in.

After entering the EDC, there will be a list of sites that you currently have access to. You can either select the site to view a list of patients for that site or you can use the search bar at the top to look up a specific patient. Change the dropdown to "Subject" and typing the ID in the search bar. You can also view a complete list of patients that you have access to by selecting "Subject" from the drop down and clicking on the search icon with the search bar blank

After you have selected a patient, the list of available folders will be on the left side of the page. The very first folder on the list will be titled "**Electronic Signature Page**". Clicking on that folder will open up the Electronic Signature Page form.

The following steps will be required to sign off on the data for each patient:

- Review the data that has been submitted up through the clinical cutoff date specified on the Electronic Signature form.

Other folders and forms can be accessed using the menu on the left side of the patient's homepage as above.

- Once you are ready to sign, **check the box** on the form and select "Sign and Save".
- You will be prompted to enter your iMedidata username and password as an electronic signature. This is the same username and password that you used to login originally. Then select "eSign".
- You will then be directed back to the Electronic Signature Page with two confirmations of the signature - a yellow banner at the top and a blue banner at the bottom specifying who signed and the time stamp.
- Repeat these steps for all applicable patients on your list.