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Title: Checkpoint Inhibitor and Radiation Therapy in Bulky, Node-Positive Bladder Cancer (CIRTiN-BC): A Phase II, Single-Arm Trial

Principal Investigator(s): Solomon Woldu, M.D.

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Checkpoint Inhibitor and Radiation Therapy in Bulky, Node-Positive Bladder Cancer (CIRTiN-BC): A Phase II, Single-Arm Trial

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Study Drug/Treatment: PULSAR (Personalized ULtrafractionated Stereotactic Adaptive Radiotherapy)

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version #_____

PROTOCOL TITLE

Checkpoint Inhibitor and Radiation Therapy in Bulky, Node-Positive Bladder Cancer (CIRTiN-BC): A Phase II, Single-Arm Trial

Principal Investigator (PI) Name: **__Solomon Woldu, M.D.____**

PI Signature: _____

Date: _____

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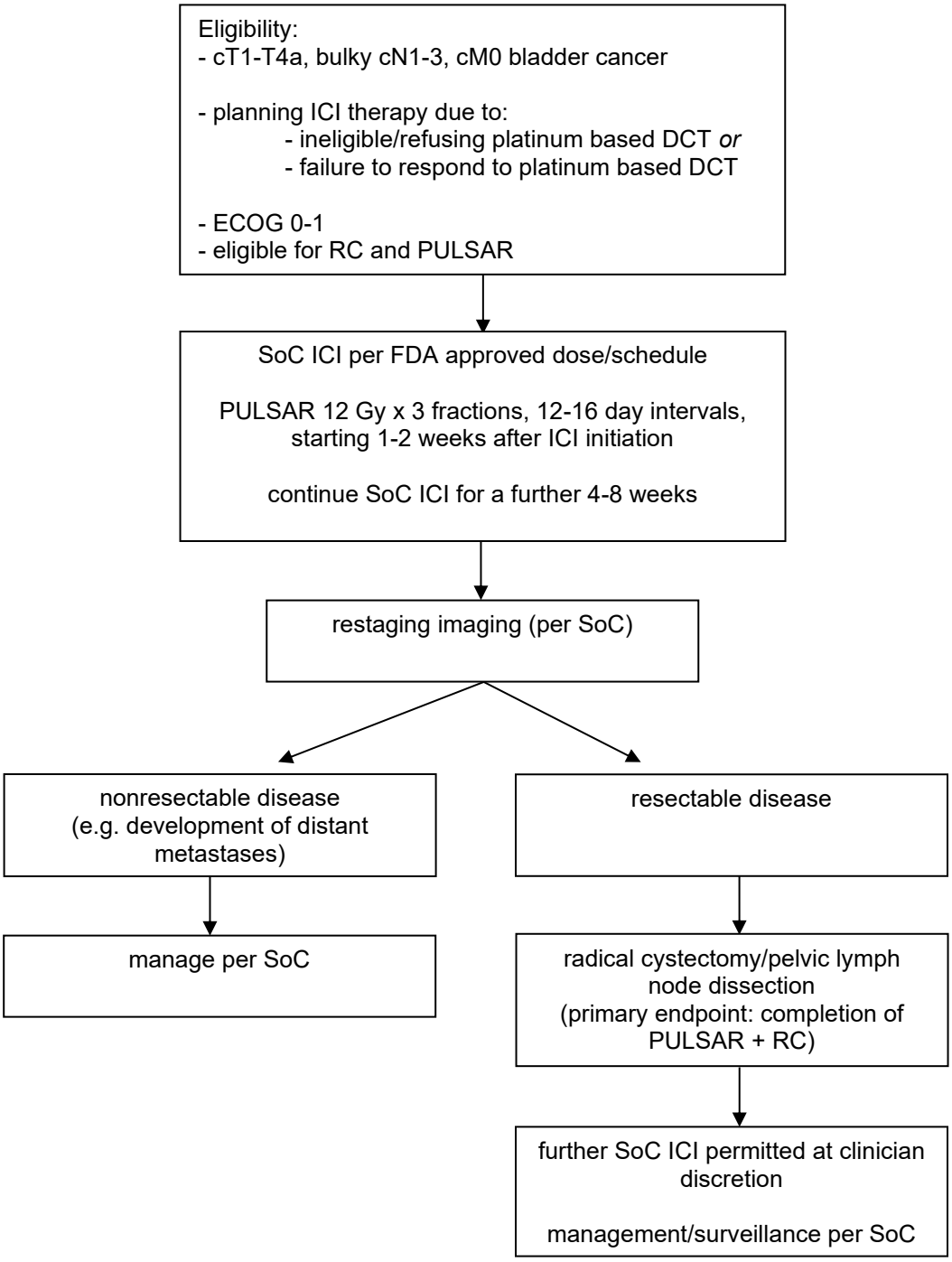
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
cN+	Clinically Node-Positive
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCT	Downstaging chemotherapy
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
ICI	Immune Checkpoint Inhibitor
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MIBC	muscle invasive bladder cancer
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NACT	Neoadjuvant chemotherapy
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
PULSAR	Personalized ULtrafractionated Stereotactic Adaptive Radiotherapy

RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence Free Survival
SAbR	Stereotactic Ablative Radiotherapy
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SoC	Standard of Care
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Checkpoint Inhibitor and Radiation Therapy in Bulky Node-Positive Bladder Cancer (CIRTiN-BC): A Phase II, Single-Arm Trial
Short Title	CIRTiN-BC
Protocol Number	STU-2021-0114
Phase	Phase I/II
Methodology	Single-arm safety/efficacy trial
Study Duration	36 months
Study Center(s)	Single center at UT Southwestern Medical Center, with potential expansion to Parkland Hospital and John Peter Smith Hospital
Objectives	To evaluate the safety and efficacy of PULSAR in patients with bulky node-positive bladder cancer on immune checkpoint inhibitor therapy due to ineligibility for or failure to respond to downstaging chemotherapy
Number of Subjects	27
Diagnosis and Main Inclusion Criteria	bladder cancer with bulky regional lymph node metastases, planning immune checkpoint inhibitor therapy due to ineligibility for downstaging chemotherapy or failure to respond to downstaging chemotherapy
Study Product(s), Dose, Route, Regimen	PULSAR (personalized ultrafractionated stereotactic ablative radiotherapy) 30 Gy in 3 fractions
Duration of administration	3 fractions at 12 - 16 day intervals
Reference therapy	standard of care with systemic therapy alone, followed by radical cystectomy if treatment response
Statistical Methodology	Proportion of patients completing the study will be calculated and the trial will be deemed successful if the number of patients completing the protocol exceeds the futility threshold of 60%. Progression-free survival, the secondary endpoint, will be estimated by the Kaplan-Meier method and compared with historic controls using the log-rank test.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Muscle invasive bladder cancer (MIBC) has high metastatic potential and warrants aggressive treatment. Standard-of-care treatment in MIBC involves platinum-based neoadjuvant chemotherapy (NACT) followed by radical cystectomy (RC) with pelvic lymph node dissection (PLND) and urinary diversion[1–3]. Bladder-conserving chemoradiation therapy is an appropriate alternative in select patients, though it is used in only a minority of cases in the United States[4]. Bladder cancer carries significant morbidity and mortality and has been cited as the most expensive malignancy to manage, on a per-patient basis, in the United States[5,6].

Metastatic spread to regional lymph nodes is an adverse prognostic factor in bladder cancer. In several large case series reported without use of neoadjuvant chemotherapy, patients with pathologically positive lymph nodes (pN+) at radical cystectomy had 5-year overall or disease-specific survival rates of only 22-30%[7–10]. The addition of neoadjuvant chemotherapy (NACT) or downstaging chemotherapy (DCT) in patients with clinically positive lymph nodes (cN+) improves outcomes, particularly in those who achieve a pathologic complete response to DCT[11,12]. However, patients who fail to respond to downstaging or neoadjuvant chemotherapy have an especially poor prognosis, with a 5-year overall survival rate of only 16% in one recent series[13]. It should also be noted that a significant proportion (up to 25-50%) of patients with bladder cancer are ineligible for chemotherapy due to medical comorbidities[14].

We recently reviewed the outcomes of patients undergoing radical cystectomy at UT Southwestern with bulky cN+ bladder cancer[15]. Among the subset of patients who did not receive or failed to respond to DCT, the 2-year progression-free survival was only 30%, despite aggressive salvage treatment. Importantly, a majority of patients (84%) in the study received downstaging chemotherapy and all were medically eligible for chemotherapy. This suggests that chemo-ineligible patients presenting with cN+ disease were not offered curative treatment. Direct comparisons with historic literature are difficult, due to widely varying definitions of cN+ disease; however, the progression-free survival of our bulky cN+ cohort closely parallels that of the cN2-3 and cM1a cohorts within one large published series[11], confirming that our bulky cN+ cohort represents an especially high-risk population.

From the preceding data it is apparent that patients with cN+ bladder cancer who are ineligible for or who fail to respond to downstaging chemotherapy are an unfortunate group with particularly poor outcomes. One potential avenue for improvement is the combination of stereotactic ablative radiotherapy (SAbR) and immune checkpoint inhibitor (ICI) as downstaging therapy prior to radical cystectomy. We anticipate that patients will benefit from the demonstrated anti-tumor effects of both treatment modalities. Additionally, combining the immunomodulatory effects of SAbR with the stimulatory effects of ICI may result in a synergistic effect more beneficial than either modality alone.

1.2 Stereotactic Ablative Radiotherapy (SAbR) and Personalized Ultrafractionated Stereotactic Adaptive Radiotherapy (PULSAR)

Stereotactic Ablative Radiation (SAbR), also known as Stereotactic Body Radiation Therapy (SBRT), is defined by the American Society of Radiation Oncology as a precise and specialized form of cancer treatment “whereby high doses of radiation are delivered

in large fraction sizes over a short course of treatment, generally limited to 5 or fewer fractions."[16] Metastasis-directed therapy with SAbR has attracted interest in a variety of malignancies due to promising early clinical results and a favorable toxicity profile. In the Phase II SABR-COMET trial, patients with cancer (primarily breast, lung, colorectal, and prostate) and up to five sites of metastasis were randomized to receive metastasis-directed SAbR (8-30 Gy in 1-10 fractions) versus standard of care. The use of SAbR resulted in an improvement in 5-year overall survival from 18% to 42% (p = 0.006) and in 5-year progression-free survival from ~3% to 17% (p = 0.001)[17]. Grade ≥2 adverse events were noted in 29% of patients and treatment-related deaths in 4.5%[18].

In the Phase II ORIOLE trial, men with prostate cancer and 1-3 sites of metastatic disease were randomized to receive metastasis-directed SAbR (20-48 Gy in 3-5 fractions) versus standard of care. SAbR resulted in improved progression-free survival (median not reached vs 5.8 months, p = 0.002) with no grade ≥3 toxic events[19]. These results of these trials support a significant recurrence-free and overall survival benefit for metastasis-directed SAbR in oligometastatic cancer.

There is limited data on the use of metastasis-directed treatment in urothelial carcinoma. In one report, 22 patients with oligometastatic urothelial carcinoma (64% with regional lymph node metastases) underwent conventional intensity-modulated radiation therapy (25-56 Gy) and achieved long-term (≥ 6 yrs) survival in 36%, with most representing patients with pelvic nodal disease[20]. In another series, 19 patients with metastatic urothelial carcinoma received SAbR to a total of 25 different metastatic lesions and achieved a local control rate of 68%. No grade ≥3 toxic events were noted. More recently, in a small Phase I trial, patients with metastatic urothelial carcinoma received SAbR (24 Gy in 3 fractions) to a single metastatic lesion, either concurrently or sequentially with the immune checkpoint inhibitor pembrolizumab. One patient (6%) experienced a grade 3 adverse event. Four out of nine patients (44%) in the concurrent-treatment group had a clinical response in sites of disease other than the irradiated lesion[21].

The use of SAbR in pelvic lymph nodes has been extensively described in the prostate cancer literature. Roughly 60% of the patients in the aforementioned ORIOLE trial had lymph node-only metastases and, as mentioned, none suffered major toxic events[19,22]. The Phase II STOMP trial, in which 55% of patients had node-only metastases and 81% of patients in the intervention arm received SAbR, likewise reported no grade ≥2 adverse events[22]. Two additional retrospective case series recently described outcomes in patients undergoing SAbR for oligometastatic prostate cancer. In one series, 94 patients underwent SAbR (median 24 Gy in 3 fractions) to pelvic lymph nodes with a 14% rate of grade 1-2 toxicity and no grade ≥3 events[23]. In a second series, 40 patients received SAbR (35-40 Gy in 5 fractions) to various sites of nodal metastasis (nearly all within the pelvis) with a single case of grade 2 and a single case of grade 3 toxicity[24]. Based on these results, use of SAbR in pelvic lymph nodes appears to be safe and well tolerated, with only minimal toxicity.

A further refinement beyond conventional SAbR, developed at UT Southwestern, is personalized ultrafractionated stereotactic adaptive radiotherapy (PULSAR). PULSAR adapts to tumor shrinkage, minimizing radiation-associated side effects. The PULSAR dose schedule mimics the vaccine booster regimen by spacing out treatments, allowing for a full cycle of antigen presentation and immune response to occur before successive doses of radiation.

In this trial, we propose a shift in the paradigm in how radiotherapy is combined with immunotherapy. Current standards of delivering SAbR entail delivering 1 to 5 fractions, consecutively daily or every other day. We hypothesize that the delivery of radiotherapy can be optimized in patients receiving immunotherapy and propose a radiotherapy

paradigm, which we termed: Personalized Ultra-fractionated Stereotactic Adaptive Radiotherapy or PULSAR.

PULSAR sets its premise on delivering radiotherapy over intentionally longer, infrequent intervals between each radiation treatment, in contrast to historical schedules (i.e. daily fractions) in an effort to activate the immune system and avoid the potentially immunosuppressive effect from ablative radiotherapy. The interval between each fraction can be irregular, episodic, or triggered, depending on the response profile for each individual patient and can elicit additional tumor kill as well as an in situ vaccination booster, which, in combination with systemic immunotherapy, can synergize and improve disease control. Moreover, each radiotherapy fraction can be adapted in real time, depending on changes with the patient and disease status (e.g. anatomy, tumor microenvironment, systemic markers, patient status). This novel radiation treatment strategy has been supported by preclinical data in murine studies performed by our group (manuscript in preparation).

To our knowledge, the neoadjuvant use of SBRT with the new PULSAR regimen or without concomitant use of immune checkpoint inhibition for bladder cancer has not been studied previously. We will conduct our study of PULSAR in patients with locally advanced bladder cancer, as PULSAR is suited to target and kill primary and nodal sites, while providing an opportunity to prime the immune system with novel tumor-associated antigens and vaccinate the immune system in situ.

1.3 Immune Checkpoint Inhibitor Therapy

Immune checkpoint inhibitor (ICI) therapy has assumed increasing importance in the management of bladder cancer. ICI agents function to nonspecifically stimulate the patient's immune response and decrease tumor immune evasion by inhibiting negative regulators of the immune response. In bladder cancer, most interest has attached to monoclonal antibodies which block the immunosuppressive surface receptor PD-1 or its ligand PD-L1[25].

Three PD-1 or PD-L1 inhibitors (avelumab, nivolumab, and pembrolizumab) are FDA-approved for second-line use in platinum-refractory advanced bladder cancer, based on clinical trials which showed objective response rates of 15-20%[26–30]. Two agents (atezolizumab and pembrolizumab) are FDA-approved for first-line use in patients who are ineligible for platinum-based chemotherapy, based on clinical trials showing objective response rates of 25-30% in this setting[31,32]. Finally, avelumab has recently gained FDA approval for use as maintenance therapy following initial response to chemotherapy in advanced/metastatic bladder cancer, with clinical trials demonstrating an improvement in median overall survival from 14 to 21 months[33].

More recent efforts have explored a role for ICI treatments in the neoadjuvant setting. Two clinical trials, ABACUS and PURE-01, explored the use of neoadjuvant atezolizumab and pembrolizumab respectively, and reported pathologic complete response (pCR, meaning ypT0 N0) rates of 31% and 37%, respectively[34,35]. While several other ongoing trials exist in this space, only a single trial has enrolled significant numbers of patients with clinical node-positive disease. In this trial, NABUCCO, patients with cN+ disease represented 42% of total enrollment. Neoadjuvant treatment with dual ICI agents (the PD-1 inhibitor nivolumab and the CTLA-4 blocker ipilimumab) resulted in an overall pCR rate of 46%[36].

Given their widespread clinical use in bladder and other malignancies, the adverse effect profile of ICI agents is well characterized. In the second-line trials cited above, for example, grade ≥3 adverse events occurred in 5-18% of patients and most notably

included autoimmune reactions at various sites including pneumonitis, colitis, and hepatitis[26–30].

In addition to the well described direct anti-tumor effects of SAbR and ICI treatment, mounting preclinical and clinical evidence also suggests a synergistic effect of the two modalities. SAbR has multiple immune-stimulating properties, including the induction of immunogenic tumor cell death and initiation of tumor antigen presentation[37–40]. Furthermore, SAbR causes local inflammation, which attracts dendritic cells to the tumor, thereby improving tumor neoantigen presentation[41,42]. The promotion of immune anti-tumor activity by radiation has been linked to increased expression of tumor-infiltrating immune cells and MHC class I, dendritic cell activation and enhanced tumor antigen cross-presentation, T-cell receptor repertoire expansion, and increased PD-L1 expression. Therefore, therapy with SAbR, which increases PD-L1 expression by both the tumor and the immune cells, has the potential to induce responses in those patients that do not respond or progress after an initial response to an ICI. As discussed above, the PULSAR technique is designed to further improve the immunomodulatory properties of SAbR.

1.4 Study Rationale

The proposed study is a Phase I/II, single arm, single institution trial of PULSAR (next-generation SAbR) therapy prior to radical cystectomy in patients with bulky, clinically node positive bladder cancer who are planned to initiate ICI due to ineligibility for platinum-based chemotherapy or failure to achieve complete clinical response to platinum-based chemotherapy. Current NCCN guidelines recommend “downstaging systemic therapy” (i.e., downstaging chemotherapy and/or ICI) for such patients as standard of care, with consolidation radical cystectomy in patients who respond to treatment[43]. However, our recent institutional experience demonstrates that even patients who do undergo radical cystectomy have poor outcomes, and patients who are medically ineligible for systemic chemotherapy are likely not being offered curative treatment at all[15]. Unfortunately, despite poor outcomes in cN+ patients, they are frequently excluded from clinical trials. For example, of the numerous trials involving the use of ICI agents in the neoadjuvant setting, only one (NABUCCO) enrolled significant numbers of cN+ patients and these still amounted to less than 50% of the total[36]. There is therefore an urgent need for new clinical trials in this space.

Stereotactic ablative radiotherapy (SAbR) and immune checkpoint inhibitor (ICI) therapy both have demonstrated anti-tumor effects in the metastatic setting, as well as favorable and well characterized safety profiles. The rationale for adding PULSAR (next-generation SAbR) to ICI is that 1) the additive effect of both modalities is likely greater than either modality alone; 2) the morbidity and recovery period of radical cystectomy frequently preclude patients from receiving additional lines of treatment, and additional treatments are therefore likely best given prior to surgery; and 3) as detailed above, PULSAR may potentiate the effects of ICI by increasing tumor neoantigen exposure to immune surveillance and by increasing levels of PD-L1 expression within the tumor, thus enhancing response to ICI.

The rationale for proceeding with radical cystectomy after ICI + PULSAR treatment is that 1) radical cystectomy remains the standard of care in patients who respond to treatment and is felt to be the only potentially curative option in advanced disease; 2) cystectomy will debulk the primary tumor, thus reducing disease burden as well as the systemic effects of the immunosuppressive tumor microenvironment; and 3) other modalities including repeat transurethral resection and imaging are not sufficiently predictive of a complete response to treatment to justify omission of cystectomy[44].

Patients will be restaged prior to radical cystectomy and those with disease deemed unresectable (e.g., interval development of distant metastases or unacceptably high surgical risk) will be managed according to the standard of care for metastatic disease, i.e., without curative intent. It should be noted that patients on ICI frequently experience a "pseudoprogression" phenomenon in which tumor size transiently increases following treatment initiation due to tumor immune infiltration[45]. Patients will therefore not be excluded from undergoing cystectomy solely on the basis of enlarging pelvic lymph nodes after ICI and RECIST criteria will not be applied in this setting.

In confining our analysis to patients with platinum-ineligible or platinum-refractory bulky cN+ disease, we wish to focus on a subset of patients with particularly poor outcomes and limited access to other modalities of treatment. Our hope is that combined-modality treatment with ICI + PULSAR + RC will increase the proportion of patients with bulky cN+ disease who undergo curative treatment, improve rates of pathologic complete response (pCR) prior to surgery, reduce rates of disease recurrence (which, in the context of bladder cancer, is an excellent proxy for cancer-specific survival), and ultimately improve patient quality of life without increasing short-term surgical complications.

1.5 Correlative Studies

No correlative studies are planned.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the feasibility of radical cystectomy after ICI + PULSAR in bulky cN+ bladder cancer patients who are ineligible for or fail treatment with platinum based chemotherapy.

2.2 Secondary Objectives

2.2.1 To determine the 2-year progression-free survival (PFS) in patients with cN+ bladder cancer in all enrolled patients, and in the subset of patients completing the full protocol of ICI + PULSAR + RC.

2.3 Primary Endpoints

2.3.1 The primary endpoint of the study is feasibility of RC after ICI + PULSAR, defined as the proportion of enrolled patients who complete three courses of PULSAR followed by radical cystectomy while remaining on ICI therapy, within sixteen weeks of initiation of PULSAR. It is anticipated that reasons for protocol non-completion may include progression to nonresectable disease and patient intolerance of treatment.

2.4 Secondary Endpoints

2.4.1 Progression free survival (PFS): Primary disease progression will be defined as any of the following. Progression-free survival will be measured from the date of the first PULSAR treatment.

1. Emergence of new sites of disease or locoregionally recurrent disease as defined by RECIST 1.1 criteria.

2. Pathologic demonstration of recurrent or metastatic disease (e.g. core needle biopsy, fine needle aspirate, diagnostic pericentesis).
3. Initiation of a patient on palliative or salvage treatment due to clinical concern for disease progression.
4. For patients with intraoperative concern for grossly incomplete disease resection (R2), the date of the first postoperative imaging study showing disease progression by RECIST 1.1 criteria (i.e., 20% increase in the sum of the diameters of all lesions, with an absolute increase of at least 5 mm; or the appearance of any new lesion).

3.0 SUBJECT ELIGIBILITY Subject Eligibility

Eligibility waivers are not recommended; however, if warranted, prior approvals are required per Section 11.6.1. Subjects must meet all inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Once registered, a subject is still required to meet all inclusion and exclusion criteria on the first day of treatment, prior to treatment.

3.1 Inclusion Criteria

3.1.1 Bladder cancer, confirmed pathologically on transurethral resection of bladder tumor (TURBT) or on bladder biopsy. Pure urothelial, variant urothelial, or any proportion of squamous cell carcinoma are permitted. Questions about eligibility may be resolved by consultation with UTSW pathology but formal pathologic review is not required.

3.1.2 Bulky, clinically node positive disease (cN+) defined as: 1) a single pelvic lymph node of ≥ 1.5 cm largest diameter on CT or MRI; *or* 2) multiple pelvic lymph nodes ≥ 1 cm largest diameter on CT or MRI. Pathologic confirmation is not required. Imaging to establish eligibility must have been obtained no more than 60 days prior to trial enrollment. The scans must be personally reviewed by the enrolling clinician. For imaging studies obtained outside of UT Southwestern, imaging review of node status and sign off by the enrolling investigator is required. Review and sign off by a UTSW radiologist is optional in ambiguous or questionable cases, but is not mandatory.

3.1.3 Age ≥ 18 years.

3.1.4 ECOG performance status 0-1.

3.1.5 Appropriate candidate for radical cystectomy, as determined by the treating urologist.

3.1.6 Appropriate candidate for stereotactic ablative radiotherapy, as determined by the treating radiation oncologist.

3.1.7 Patient is planned to initiate or is within 1-3 weeks of initiation of FDA-approved immune checkpoint inhibitor therapy based on ineligibility to receive platinum-based downstaging chemotherapy (DCT) (Cohort 1, as detailed below) *or* failure to achieve clinical complete response to platinum-based DCT (Cohort 2, as detailed below).

Cohort 1 (chemotherapy-ineligible) – either of:

- patient staged with bulky cN+ disease as defined above, medically ineligible to receive any platinum-based chemotherapy or, after appropriate and documented counseling, refusing to receive any-platinum-based chemotherapy; *or*

- patient staged with bulky cN+ disease as defined above, medically ineligible to receive cisplatin-based chemotherapy, with PD-L1 positive tumor (according to methodology described in the FDA approval label for the respective ICI agent)

Cohort 2 (chemotherapy non-responding) – any of:

- patient, initially staged with bulky cN+ disease as defined above, with radiologic progression after two cycles of platinum-based DCT (per RECIST 1.1 criteria: ≥20% increase in summed short-axis diameter of visible lesions with ≥ 5 mm absolute increase)

- patient, initially staged with bulky cN+ disease as defined above, failing to achieve radiologic complete response after three or four cycles of platinum-based DCT (failure of all enlarged lymph nodes to decrease to < 1 cm short-axis diameter)

- patient, initially staged with bulky cN+ disease as defined above, failing to achieve radiologic complete response after one or two cycles of platinum-based DCT which was discontinued due to patient intolerance

- patient, initially <u>not</u> staged with bulky cN+ disease as defined above, who progresses to cN+ disease as defined above after two or more of cycles of platinum-based DCT

3.1.8 Permitted downstaging chemotherapy regimens are gemcitabine/cisplatin (gem/cis), gemcitabine/carboplatin (gem/carbo), and methotrexate/vinblastine/doxorubin/cisplatin (MVAC, in any dose variant).

3.1.9 Permitted immune checkpoint inhibitor agents are those FDA-approved for platinum-ineligible (Cohort 1) or platinum-refractory (Cohort 2) bladder cancer: atezolizumab or pembrolizumab for Cohort 1; avelumab, nivolumab, or pembrolizumab for Cohort 2. If additional immune checkpoint inhibitor (anti-PD1, anti-PD-L1, and/or anti-CTLA4) agents are approved for use in advanced urothelial carcinoma during the study, these agents will be permitted as well.

3.1.10 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 *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.11 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Medical or anatomic contraindication to any of the study treatment modalities (radical cystectomy, stereotactic ablative radiotherapy, immune checkpoint inhibitor therapy).

3.2.2 Non-urothelial histology (other than pure squamous cell, which is permitted) including pure adenocarcinoma, pure small cell carcinoma, sarcoma, lymphoma, non-genitourinary primary (e.g. colorectal).

3.2.3 Metastatic (cM1) disease, defined as 1) lymph nodes ≥ 1 cm above the aortic bifurcation (cM1a), *or* metastases to bone, brain, or any visceral site (cM1b). Patients with a single enlarged retroperitoneal lymph node will be eligible with an adequately performed lymph node biopsy showing no metastatic disease or with a PET scan showing absence of FDG avidity.

3.2.4 Second primary malignancy, except: 1) non-metastatic (cM0) prostate cancer, 2) non-metastatic (cM0) endometrial cancer, 3) non-melanoma skin cancer, 4) cervical squamous cell carcinoma *in situ*, 4) any AJCC Stage I/II or organ-confined primary malignancy for which the patient has undergone curative treatment and has been without evidence of disease for three years.

3.2.5 Prior pelvic radiation therapy.

3.2.6 Autoimmune disease rendering the patient ineligible for ICI.

3.2.7 Treatment with any immunosuppressive agent within 14 days of study entry, excluding topical or inhaled corticosteroids or adrenal-replacement steroids.

3.2.8 End stage renal disease requiring dialysis.

3.2.9 HIV infection, unless stable on HAART with CD4+ count > 400.

3.2.10 Subjects may not be receiving any other investigational agents for the treatment of the cancer under study.

3.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab, or other agents used in study.

3.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (other than atrial fibrillation / atrial flutter), or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.

3.2.13 Subjects must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

4.0 TREATMENT PLAN

4.1 PULSAR: Dose and Techniques

Patients are eligible for the trial if they have bulky, clinically node-positive (cN+) bladder cancer and have either recently initiated (within ≤ 1 week) or are planned to initiate immune checkpoint inhibitor (ICI) therapy due to either 1) ineligibility for/refusal of platinum-based downstaging chemotherapy; or 2) failure to achieve a complete clinical response to platinum-based downstaging chemotherapy. Patients will initiate PULSAR treatment 1-2 weeks after initiating ICI. PULSAR will be administered in 3 fractions of 12 Gy each (36 Gy total) at 12-16 day intervals and patients will undergo radical cystectomy with bilateral extended pelvic lymph node dissection within 4-8 weeks after completion of PULSAR. ICI therapy will be administered according to the FDA-approved dosing route and schedule and will be continued during PULSAR treatments.

PULSAR treatment will be initiated 1-2 weeks after the patient is initiated on an FDA-approved ICI agent. PULSAR will be administered in 3 fractions of 12 Gy each at 12-16 day intervals. Target areas will include the region of the bladder containing the primary tumor (confirmed, if necessary, on office flexible cystoscopy at UTSW) and to up to five targetable, pathologically enlarged bulky lymph nodes (as deemed feasible by the treating radiation oncologist). Non-enlarged pelvic lymph nodes will be spared to minimize adverse effects on the tumor immune response.

4.1.1 PULSAR will be delivered with the targeting, planning, and directing of treatment fields guided to a target based on known 3D coordinates related to reliable fiducial markers. This differs from conventional radiation therapy in which treatment is guided by skin or bony landmarks assumed to correlate to the target volume based on the initial simulation. Treatment will account for inter/intra-fractional errors with careful dosimetry that delivers an ablative dose to the involved lesions while respecting normal tissue constraints. In the event that fiducial placement is deemed unfeasible or unsafe, or would result in an unacceptable delay in treatment, fiducial placement may be omitted and targeting based on a combination of pre-treatment imaging and findings on flexible cystoscopy.

4.1.2 Radiation Therapy Prescription Dose

The treating radiation oncologist can choose to deliver 10 or 12 Gy per fraction depending on the clinical circumstances, i.e. anatomical location and adjacent organs-at-risk. Each radiation therapy fraction will encompass the 95% of the planning target volume, and is considered compliant to the protocol. The following table lists the acceptable range of dose per fraction, with preference for the higher dose if safely achievable. Any dose delivered that is beyond the recommended doses will be considered an unacceptable variation.

Number of fractions	Dose per fraction	Total dose
3	10-12 Gy	30-36 Gy

4.1.3 Prescription Interval

Each PULSAR fraction may be delivered every 2 weeks to potentiate the synergy between ICI and radiotherapy, until the completion of the prescribed number of fractions. PULSAR may be held if the patient does not have any targetable disease. Each PULSAR treatment and date of treatment delivery will be recorded.

4.1.4 Radiation Treatment Concerns and Concurrent Medications

Analgesic premedication to avoid general discomfort during long treatment durations is recommended when appropriate.

4.2 Technical Factors and Considerations

4.2.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-15 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Restriction of photon beam energies > 10 MV but less than 15 MV will be based on clinical appropriateness taking into account distance the beam must travel to the target.

4.2.2 Dose Verification at Treatment

In-vivo dosimeter measurements (e.g., diode, TLD) may be obtained for surface dose verification for accessible beams. This information is not required by the protocol.

4.2.3 Treatment Platforms

The trial allows most commercially available photon or proton producing treatment units. Treatment units should include image guidance. Both 3D conformal and intensity-modulated radiation therapy (including volumetric-modulated arc therapy (VMAT)) are allowed. Proton or other charged particle units are not allowed in this study. Other specialized accelerators (e.g., the CyberKnife® or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol.

4.3 Simulation and Image Guidance

4.3.1 Patient Positioning

Patients will be positioned in a stable position that allows accurate reproducibility of the target between treatments. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to ensure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) with any significant probability (i.e. < 5%).

4.3.2 Image Guidance

Isocenter or reference point port localization images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (i.e. isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices or cone-beam CT equipment. For treatment systems that use kV imaging but also allow EPID imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained.

4.4 Treatment Planning and Target Volumes

4.4.1 Image Acquisition

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the

patient anatomy and fiducial system for stereotactic targeting. CT scan with IV contrast is recommended unless the patient has allergy to contrast or renal insufficiency. Axial acquisitions will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers.

4.4.2 Target Volumes

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume at the primary site (GTVp) and nodal site(s) GTVn. The targets will generally be drawn using appropriate windowing based on location of the primary tumor and metastatic lymph nodes. Given that this treatment will adapt to changes in tumor dimension, the clinical target volume (CTV) will correspond to the GTVp/GTVn with no added margin. A 5 mm planning target volume (PTV) margin will be added to account for setup and intermal motion.

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4.5 Dosimetry

4.5.1 Intensity Modulated Radiation Therapy (IMRT)

IMRT, including volumetric-modulated arc therapy (VMAT) and modulated charged particles is allowed in this study. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized, and the area of each segment should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam's eye view).

4.5.2 Dose Calculations

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction.

Successful treatment planning will require accomplishment of all of the following criteria:

1. Maximum dose: The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
2. Prescription isodose: The prescription isodose surface must be ≥ 60% and < 90% of the maximum dose.
3. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V95%RX = 100%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX > 99%).

4.6 Normal Tissue Dose Constraints

4.6.1 The following table lists the specific organ and dose fractionation constraints on normal tissue. Given the irregular, long intervals between each radiotherapy fraction, total dose will be calculated to a particular organ-at-risk to ensure safety of radiation therapy. Exceeding these dose tolerances by more than 2.5%

constitutes a minor protocol violation. Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

Three Fraction

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	15.3 Gy	17.4 Gy	neuritis
Cochlea			14.4 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	15.9 Gy	23.1 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc	15.9 Gy	22.5 Gy	myelitis
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	neuritis
Sacral Plexus	<5 cc	22.5 Gy	25.5 Gy	neuropathy
Esophagus*	<5 cc	27.9 Gy	32.4 Gy	esophagitis
Brachial Plexus	<3 cc	22 Gy	26 Gy	neuropathy
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis
Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	39 Gy	43 Gy	impairment of pulmonary toilet
Bronchus- smaller airways	<0.5 cc	25.8 Gy	30 Gy	stenosis with atelectasis
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc	22.5 Gy	30 Gy	ulceration
Jejunum/Ileum*	<30 cc	20.7 Gy	28.5 Gy	enteritis/obstruction
Colon*	<20 cc	28.8 Gy	45 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	43 Gy 30.3 Gy	47 Gy	proctitis/fistula
Ureter			40 Gy	stenosis
Bladder wall	<15 cc	17 Gy	33 Gy	cystitis/fistula
Penile bulb	<3 cc	25 Gy		impotence
Femoral Heads	<10 cc	24 Gy		necrosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc for males and 950cc for females***	10.8 Gy		Basic Lung Function
Lung (Right & Left)			V-11.4Gy<37%	Pneumonitis
Liver	700 cc***	17.7 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc***	14.7 Gy		Basic renal function

***Avoid circumferential irradiation**
**** "point" defined as 0.035cc or less**
*****or one third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater**

4.7 Radiation Therapy Quality Assurance

Drs. Iyengar and Vo will perform a radiation therapy quality assurance review after complete data of the first 10 cases enrolled at the University of Texas Southwestern Medical Center followed by a final review after complete data for the remaining cases are completed. These cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

4.8 Concomitant Medications/Treatments

Any ICI agent approved for use in advanced urothelial carcinoma may be used in this study. Currently approved agents for use in the second line setting (i.e., after chemotherapy or Cohort 2) include atezolizumab, avelumab, duvalumab, nivolumab, and pembrolizumab. Approved agents for use in the first line setting (i.e., in chemotherapy-ineligible or Cohort 1) include atezolizumab and pembrolizumab. Patients are eligible if they are planned to initiate ICI, or if they are within 1-3 weeks of initiation of an approved ICI agent. Subjects should receive at least two, and may receive up to four, doses of ICI concurrent with PULSAR prior to undergoing surgery. PULSAR will be initiated no less than one week after receipt of the first dose of ICI.

This use of ICI is considered a standard of care therapy. The drug will be administered and managed by the treating medical oncologist. Continuation beyond the study period per standard of care is at the discretion of the treating medical oncologist. If additional immune checkpoint inhibitor (anti-PD1, anti-PD-L1, and/or anti-CTLA4) agents are approved for use in advanced urothelial carcinoma during the study, these agents will be permitted as well. If FDA approval is withdrawn or if agents are voluntarily withdrawn by the manufacturers for the relevant clinical indications, the agents will not be permitted for new study enrollments. Patients already on such agents will be permitted to remain in the study. Switching from one approved agent to another while on the study is permitted at the treating clinician’s discretion.

4.9 Other Modalities or Procedures

No other modalities of treatment are planned. Patients are expected to receive any and all indicated interventions according to the usual standard of care.

4.10 Duration of Therapy

The trial therapy will be considered complete when patients finish the third of three fractions of PULSAR. “In the absence of treatment delays due to adverse events, treatment may continue until that point or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient’s condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.11 Duration of Follow Up

All follow up after radical cystectomy represents the standard of care. Patients will be followed for adverse outcomes for 90 days following radical cystectomy. After that point, subjects will only be followed for progression-free and overall survival for two years from the date of first PULSAR treatment or disease recurrence, whichever occurs first.

4.12 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.13 Subject Replacement

Any subjects removed from the study that have not completed at least one fraction of radiation should be replaced by additional recruitment of study subjects.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 60 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Medical history

Complete medical and surgical history, history of infections

5.1.3 Demographics

Age, gender, race, ethnicity

5.1.4 Review subject eligibility criteria

5.1.5 Review previous and concomitant medications

Including history of chemotherapy and history of any antibiotic treatment within three months of study enrollment

5.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 Performance status

Performance status evaluated prior to study entry according to Appendix A.

5.1.8 Hematology

Complete blood count with differential.

5.1.9 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.10 Pregnancy test (for females of child bearing potential)

See section 3.1.6.1 for definition.

5.1.11 Tumor assessment

CT or MRI of chest, abdomen, and pelvis with IV contrast, when possible. Additional imaging may be obtained at the treating clinician's discretion. Baseline imaging to determine eligibility must have been obtained within 60 days of trial enrollment.

5.2 Procedures During Treatment

5.2.1 At time of each PULSAR Fraction

- Physical exam, vital signs, history
- Toxicity assessment

5.2.2 At time of radical cystectomy

- Physical exam, vital signs, history
- Toxicity assessment

5.2.3 30 days after radical cystectomy

- Physical exam, vital signs
- Toxicity evaluation
- Hematology (standard of care)
- Serum chemistries (standard of care)

5.2.4 90 days after radical cystectomy

- Physical exam, vital signs
- Toxicity evaluation
- Hematology (standard of care)
- Serum chemistries (standard of care)
- Restaging imaging (standard of care)

5.2.5 Every 6 months x 2 years

- Chart review and/or patient contact to determine recurrence and vital status

5.3 Follow-up Procedures

Subjects will be followed at the 30 and 90 day timepoints (± 4 weeks) following radical cystectomy. After that time frame, patients will be followed

- Procedure

5.4 Time and Events Table

	Screening	PULSAR Q12-16d x 3 fractions	Post PULSAR, pre RC	Post RC (30 days)	Post RC (90 days)	Follow up q6mo x 2 yrs
Procedures						
Informed Consent	X					
Eligibility verification	X					
History and Physical Exam	X	X	X	X	X	
Performance Status	X	X	X	X	X	
(Re)staging Imaging[1]	X		X		X	
Toxicity Evaluation		X	X	X	X	
Blood Draw[2]	X	X	X	X	X	

Pregnancy Test (if applicable)[3]	X					
PULSAR treatment[4]		X				
Chart review / recurrence status						X

[1] CT or MRI with IV contrast, if possible. Imaging to determine eligibility must have been performed within **60 days of enrollment**. All imaging used within the study represents standard of care. Additional imaging may be obtained at the treating clinician's discretion.
[2] Blood draws after surgery represent standard of care
[3] Only in females of child-bearing potential, as defined in section 3.1.
[4] SAbR treatments to be administered in three fractions at 12-16 day intervals.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator);

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 MEASUREMENT OF EFFECT

6.1 Antitumor Effect

Response and progression following radical cystectomy (as distinct from criteria for trial eligibility, which are defined in section 3.1.2 above), will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) Committee [Eur J Cancer. 2009;45(2):228-247]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with PULSAR.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one PULSAR treatment, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of treatment will also be considered evaluable.)

6.1.2 Disease Parameters

Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy. For this reason, and because of the potential for pseudoprogression as discussed above, the pelvic lymph nodes will not be considered evaluable at the initial restaging scan following PULSAR and prior to radical cystectomy.

Non-measurable disease.
All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions.
All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 60 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (SLD) of target lesions, taking as reference the baseline SLD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SLD since the treatment started. There can be no unequivocal new lesions.

While on study, should a chosen Target lesion become non-evaluable, document as Not Evaluable (NE).

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

(Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

While on study, should a chosen Non-Target lesion become non-evaluable, document as Not Evaluable (NE).

6.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE

Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

A 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

6.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of PULSAR treatment to time of progression. Progression is defined as any of:

1. Radiologic disease progression, as defined by RECIST 1.1 criteria above.
2. Pathologic demonstration of recurrent or metastatic disease (e.g. core needle biopsy, fine needle aspirate, diagnostic pericentesis).
3. Initiation of a patient on salvage or palliative treatment due to clinical concern for disease progression.
4. For patients with documented concern (by the operating surgeon) for grossly incomplete disease resection (R2) including bulky unresectable lymph nodes, the date of the first postoperative imaging study showing disease progression by RECIST 1.1 criteria.

6.2 Safety/Tolerability

Analyses will be performed for all subjects having received at least one fraction of radiation. The study will use the CTCAE version 5.0 for reporting of adverse events. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.0 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are reported in a routine manner at

scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.1.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 90 days post treatment will be considered acute adverse events.

Late Adverse Events

Adverse events occurring in the time period from the end of acute monitoring, to 1 year post treatment, will be defined as late adverse events. In addition, the study team will review encounters in a select specialty category relevant to study endpoints. These select specialties include hospitalizations, medical oncology, radiation oncology, and urology records and will be limited in scope based on categorization of events (GU/GI) and also the type of records that will be queried (hospitalizations, medical oncology, and radiation oncology).

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

OHRP and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.1.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

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

Note: This includes all events that occur up to the end of the acute adverse events reporting period as defined in section 7.1.1. Any event that occurs more than 30 days after the last dose of and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.2.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record, require reporting to the DSMC regardless of whether IRB reporting is required. ***All SAEs occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s).*** In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. Electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC.

UT Southwestern and affiliates will submit documentation via the SAE submission portal. All subsites participating in multi-center study may utilize the Serious Adverse Event Template and submit to the IIT Project Manager, or designee. The DSMC Coordinator will route the form to the DSMC Chair who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required via the same process. *(See Appendix V of the SCCC DSMC Plan for instructions on how to submit SAEs through the portal and for a template Serious Adverse Event Form which may be utilized by subsites on multi-center IIT studies).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chair reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chair determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to Urology CRO, 214-645-8787
Written reports to: UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of PI awareness.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see policy_9.5reportable.pdf (utsouthwestern.edu)

7.3 Stopping Rules

If the incidence of Grade 3 or higher adverse events convincingly exceeds 50%, a threshold we are comfortable with given the potential benefit of the regimen as well as our experience in managing the side effects in this patient population, we will temporarily halt the study and carefully review the available data at that point in order to suggest a potential modification. If we determine that high rates of adverse events are intrinsically related to protocol and no modification will reasonably decrease this rate to an acceptable threshold (below 50%), then we will terminate the study.

8.0 CORRELATIVES/SPECIAL STUDIES

Patients have the option to enroll on the UTSW tissue protocol (STU 072010-098) for the collection for sera, PBMC and available tumor tissue to be collected before and during treatment. The protocol consent will include consent for use of tissues in future studies, e.g. molecular profiling.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This is a single institution, single arm, phase II trial. We hypothesize that the combination of standard-of-care ICI with PULSAR will be feasible and does not result in delays in treatment. We define a target rate of protocol completion (completion of radical cystectomy within sixteen weeks of initiation of PULSAR) of 90%, with a lower boundary of futility at 60%.

The secondary endpoint is efficacy, defined by 2-year recurrence-free survival.

As discussed above, we additionally plan to assess safety (defined by the 90-day rate of Clavien-Dindo Grade ≥ III complications following radical cystectomy); pathologic outcomes; rates of residual disease at surgery; and ureteroenteric anastomotic stricture rate.

If the incidence of Grade 3 or higher treatment-related adverse events convincingly exceeds 50%, a threshold we are comfortable with given the potential benefit of the regimen as well as our experience in managing the side effects in this patient population, we will temporarily halt the study and carefully review the available data at that point in order to suggest a potential modification. If we determine that high rates of adverse events are intrinsically related to protocol and no modification will reasonably decrease this rate to an acceptable threshold (below 50%), then we will terminate the study.

9.2 Sample Size and Accrual

For the primary endpoint of feasibility, we define a target rate of protocol completion (completion of radical cystectomy within sixteen weeks of initiation of PULSAR) of 90%, with a lower boundary of futility at 60%. A sample size of 24 patients provides 91% power to reject a 60% completion rate at a two-sided alpha of 0.05. Of note, this sample size was employed in the recent NABUCCO trial, which addressed a similar high-risk patient cohort[36]. Allowing a 10% drop out rate increases the desired enrollment to a total of **27 patients**. Given the desired enrollment of 27 patients and the three-year trial period, this will require accrual of nine patients per year across all sites.

For the secondary endpoint of progression-free survival, the trial-eligible subset of our recently published historic series of cN+ bladder cancer patients achieved a 2-year recurrence-free survival rate of 30%[15]. A sample size of 24 patients provides 90% power to detect a 27% absolute increase in 2-year recurrence free survival with a one-sided alpha of 0.10 using the Kaplan-Meier log-rank test.

9.3 Data Analyses

The primary endpoint, protocol completion, will be assessed by calculating the proportion of patients completing radical cystectomy within sixteen weeks of initiating PULSAR treatment. If the proportion of patients undergoing cystectomy exceeds 60%, the null hypothesis (that use of ICI+PULSAR+RC is not feasible) will be deemed to have been rejected.

For the secondary endpoint, progression-free survival will be determined as described above, and will be reported by means of Kaplan-Meier survival curves, median progression-free survival time, and proportion of patients without progression at two years. Comparison will be made to the trial-eligible subset of patients in a historic control series using the log-rank test. The 2-year progression-free survival rate in the historic cohort was 30%. The null hypothesis will be rejected if the one-sided *p* value for the comparison is less than 0.10.

Additional planned analyses include the following, all of which will be reported with simple descriptive statistics (*n / N* and percentage):

Major complication rate: A major surgical complication will be defined as any postoperative complication of Clavien-Dindo Grade III or higher.

Pathologic outcomes: Pathologic outcomes will be defined as follows, based on the final surgical pathology report:

1. Pathologic complete response: no viable disease remaining in the specimen (ypT0 N0).
2. Pathologic non-muscle-invasive downstaging: primary tumor without muscle invasion, and no viable disease in lymph nodes (≤ypT1 N0).
3. Pathologic organ-confined downstaging: primary tumor confined to detrusor muscle, and no viable disease in lymph nodes (≤ypT2 N0).
4. Nodal complete response: no viable disease in lymph nodes, regardless of primary tumor stage (ypTany N0).

Residual disease: Residual disease at surgery will be defined as follows:

1. Microscopic residual disease (R1) will be defined as any positive soft tissue margin on the final surgical pathology report, excluding carcinoma *in situ* at ureteral margins.
2. Gross residual disease (R2) will be defined as any grossly positive tissue margin reported on a pathology report, *or* the operating surgeon's subjective report of grossly unresectable disease including bulky matted lymph nodes.

Ureteroenteric stricture rate, defined as the need for procedural intervention performed for decompression of an obstructed kidney (e.g. percutaneous nephrostomy tube or surgical revision of ureteroenteric anastomosis), unless due to known or suspected disease recurrence.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

10.3 Registration Procedures

All subjects must be registered with the UTSW Research Office before enrollment on study.

New subjects will receive a number beginning with 01 upon study consent such that the first subject consented is numbered 01, the second subject consented receives the number 02, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 01 will become 01-01 upon enrollment. If subject 02 screen fails, and subject 03 is the next subject enrolled, subject 03 will become 03-02 and so-on.

A lead-in identifier for each study site will be used. For example, the first patient consented and enrolled at the first site will be participant 01-001-01. The second participant enrolled at the second site might be 02-003-02, and so on.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

10.4 Data Management and Monitoring/Auditing

For this trial, UTSW SCCC is using an internal secured EDC for the electronic data capture of case report forms for this SCCC Investigator Initiated Trial. This will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

Toxicity reviews will be performed annually. These reviews will be documented and reviewed annually.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and

monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

10.5 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.5.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

10.5.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, and/or
- protect the life or physical well-being of subjects or others

➢ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

10.5.3 Serious Noncompliance (**formerly called major deviations or violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- Adversely affects the integrity of the data and research (i.e. substantially compromises the integrity, reliability, or validity of the research

➢ **Reporting requirement**: Serious Noncompliance must be promptly reported to the IRB within 5 working days of PI awareness.

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10.5.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in one or more protocols simultaneously, or over a period of time) which continues after initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

➢ Reporting requirement*: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

10.5.4 Noncompliance (that is neither serious nor continuing; formerly called minor deviations: include any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance
  - **Reporting requirement**: Noncompliance that is neither serious nor continuing should be tracked and summarized in the progress report at the next IRB continuing review, or notice of study closure, whichever comes first.

10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

Appendix A. Eligibility Checklist

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INCLUSION criteria:

☐ age ≥ 18 years

☐ ECOG performance status (circle): 0 / 1

☐ bladder cancer, stage cT1 or higher: pure urothelial, urothelial variant (in any proportion), squamous cell carcinoma (in any proportion)

presence/proportion of variant histology: _____

AJCC 8th edition clinical tumor stage assigned by treating clinician: _____

☐ clinical concern for bulky node positive disease on imaging, defined as either:

☐ a single pelvic lymph node ≥ 1.5 cm largest axis diameter *or*

☐ multiple pelvic lymph nodes ≥ 1.0 cm largest axis diameter (cN2-3)

diameter of largest node: _____ cm

number of enlarged nodes: _____

date of imaging used to determine eligibility: _____ modality (circle): CT / MRI / PET

AJCC 8th edition clinical nodal stage assigned by treating clinician: _____

if radiology consultation obtained, please specify radiologist: _____

☐ ineligibility for, or failure to respond to, platinum-based downstaging chemotherapy (MVAC, gemcitabine/cisplatin, gemcitabine/carboplatin):

☐ **ineligible** for platinum chemotherapy (Cohort 1) based on (check all that apply):

☐ inadequate renal function

☐ preexisting neuropathy

☐ patient refusal after adequate counseling

☐ cisplatin-ineligible, carboplatin-eligible with positive PD-L1

☐ other medical contraindication, please specify: _____

☐ **failure to respond** to platinum chemotherapy (Cohort 2), based on:

☐ patient with bulky cN+ disease and radiologic disease progression after ≥ 2 cycles of chemotherapy

☐ patient with bulky cN+ disease and failure to achieve radiologic complete response after ≥ 3 cycles of chemotherapy

☐ patient with bulky cN+ disease failing to achieve radiologic complete response after 1-2 cycles of chemotherapy which was discontinued due to patient intolerance

☐ patient progressing to bulky cN+ disease after ≥ 2 cycles of chemotherapy

☐ plan by treating medical oncologist to initiate treatment with an approved immune checkpoint inhibitor treatment, or initiation of an approved checkpoint inhibitor within the three weeks prior to trial enrollment (please circle agent)

☐ Cohort 1 (chemo-ineligible): atezolizumab / pembrolizumab

☐ Cohort 2 (chemo-non-responding): avelumab / nivolumab / pembrolizumab

☐ candidate for radical cystectomy, as determined by treating urologist

☐ candidate for radiation therapy, as determined by treating radiation oncologist

☐ ability to provide informed consent

☐ negative pregnancy test (female of child-bearing age)

☐ agrees to use adequate contraception *or* female not of child-bearing age

EXCLUSION criteria - confirm absence of <u>all</u> of the following:

☐ pure adenocarcinoma, pure small cell carcinoma, sarcoma, lymphoma, non-genitourinary primary tumor, or other non-urothelial histology except squamous cell carcinoma

☐ metastatic disease (including lymph nodes ≥ 1 cm above the aortic bifurcation, unless accompanied by a negative lymph node biopsy or negative PET scan)

☐ second primary malignancy, except (check if applicable):

☐ cM0 prostate cancer

☐ cM0 endometrial cancer

☐ non-melanoma skin cancer

☐ cervical squamous cell carcinoma *in situ*

☐ any AJCC Stage I/II or organ-confined primary malignancy in remission for ≥ 3 years following curative treatment

☐ prior pelvic radiation therapy

☐ autoimmune disease resulting in ineligibility for immune checkpoint inhibitor

☐ treatment with an immunosuppressive agent within 14 days of study entry, except (check if applicable):

☐ topical or inhaled corticosteroids

☐ adrenal-replacement steroids

☐ end-stage renal disease requiring dialysis

☐ HIV infection, unless stable on HAART with CD4+ count of > 400

☐ receipt of other investigational agents or treatment modalities

☐ history of true allergic or anaphylactic reaction to atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab, or other similar agent

☐ uncontrolled intercurrent illness including active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (other than atrial fibrillation / atrial flutter), or psychiatric illness resulting in inability to safely undergo the study or complete study requirements

☐ pregnancy or current breastfeeding