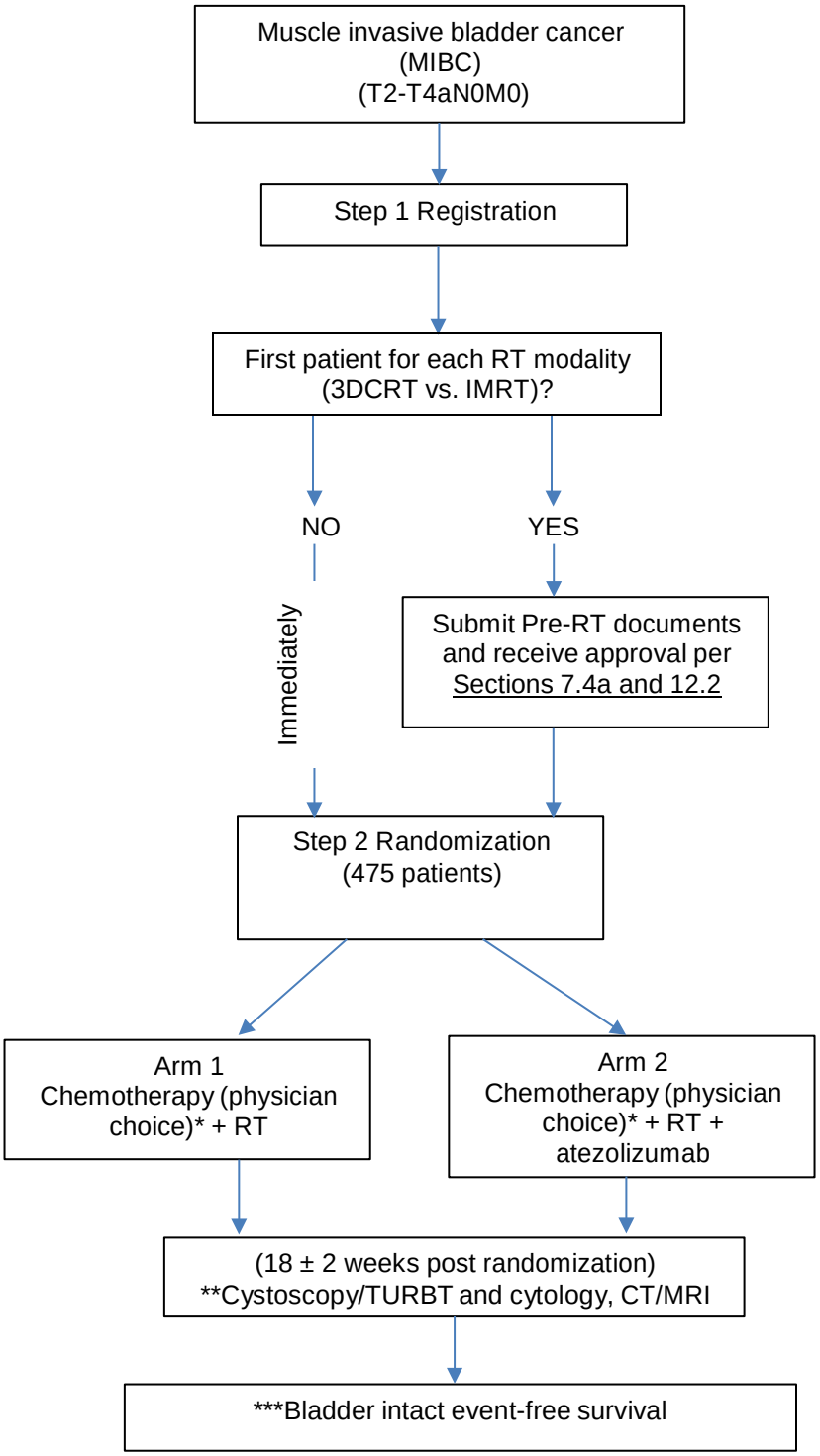
SCHEMA



* Chemotherapy regimen choices are listed in Sections 7.2 and 7.3.
** Time relative to randomization
*** Event components for bladder intact event-free survival are specified in Section 10.1.

5.0 ELIGIBILITY CRITERIA

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

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 3 weeks later would be considered Day 21. This allows for efficient patient scheduling without exceeding the guidelines. If Day 21 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

5.1 Step 1 Registration

If this will be the first patient from a registering site to receive a given RT modality (3DCRT vs. IMRT), the site must first submit pre-RT planning documents within 3 days of Step 1 registration as specified in Section 12.2 and receive approval from IROC before randomizing the patient to Step 2.

If this will not be the first patient to receive a specific RT modality, the patient should be immediately randomized to Step 2 on the same day.

5.2 Step 2 Randomization

If patient required review of pre-RT planning, randomization must occur within 14 days of initial registration.

5.3 Disease Related Criteria

a. Patients must have histologically proven, T2-T4a N0M0 urothelial carcinoma of the bladder within 70 days prior to randomization. Patients with mixed urothelial carcinoma will be eligible for the trial, but the presence of small cell carcinoma will make a patient ineligible. Patients with lymph nodes ≥ 1.0 cm in shortest cross-sectional diameter on imaging (CT / MRI) must have a biopsy of the enlarged lymph node showing no tumor involvement within 70 days prior to randomization. These patients may be suitable for neoadjuvant chemotherapy and radical cystectomy and are eligible for this trial if they seek out a bladder sparing treatment

strategy, however patients who have received prior systemic chemotherapy for bladder cancer are not eligible for the trial.

b. Patients must undergo a TURBT within 70 days prior to randomization. In a situation where a patient is referred from outside to the enrolling institution, patient must have a repeat cystoscopy by the urologist who will be following the patient on the clinical trial to assess the adequacy of the prior TURBT. Patient may then undergo repeat TURBT if deemed necessary as standard of care by the treating urologist. Patients may have either completely or partially resected tumors as long as the treating urologist attempted maximal resection. Patient must not have T4b disease.

c. Patients must undergo radiological staging within 70 days prior to randomization. Imaging of chest, abdomen, and pelvis must be performed using CT or MRI. Patients must not have evidence of T4bN1-3 disease. Eligibility is based on the local radiology report.

d. Patients with hydronephrosis are eligible if they have unilateral hydronephrosis and kidney function meets criteria specified in Section 5.3e.

e. Patients must not have had urothelial carcinoma or histological variant at any site outside of the urinary bladder within the previous 24 months except Ta/T1/Carcinoma in situ (CIS) of the upper urinary tract including renal pelvis and ureter if the patient had undergone complete nephroureterctomy.

f. Patients must not have diffuse CIS based on cystoscopy and biopsy.

5.4 Prior/Concurrent Therapy Criteria

a. Patient must be planning to receive one of the protocol specified chemotherapy regimens.

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

c. Patient must not have received any systemic chemotherapy for their bladder cancer.

d. Patient must not have had prior pelvic radiation.

e. Patients must not have received prior treatment for muscle invasive bladder cancer including neoadjuvant chemotherapy for the current tumor.

f. Patients must not have received any systemic therapy (including, but not limited to, interferon alfa-2b, high dose IL-2, PEG-IFN, anti-PD-1, anti-PD-L1), for non-muscle invasive bladder cancer. Prior *intravesical* BCG, interferon, and intravesical chemotherapy are allowed.

g. Patients must not have received any of the following prohibited therapies within 28 days prior to randomization or be planning to receive any of the following prohibited therapies during protocol treatment:

- Anti-cancer systemic chemotherapy or biological therapy not specified in the protocol.
- Immunotherapy not specified in this protocol.
- Systemic or intravesical use of any non-study anti-cancer agent (investigational or non-investigational).
- Investigational agents other than atezolizumab.

- Live vaccines: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed. Prior administration of intravesical BCG is allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids (defined as 10 mg prednisone) are acceptable, however site investigators should consult with the Study Chair for any dose higher than 10 mg prednisone. Dexamethasone 4 mg iv with chemotherapy to prevent nausea is allowed.
- RANKL infusion: Concurrent denusumab (which binds the cytokine RANKL) for any known indication is prohibited due to interaction with study medication.

h. Patients must not have a major surgical procedure within 28 days prior to randomization. If patient had any surgical procedure then they should have recovered to full presurgical performance status and surgical adverse events should have resolved to grade $\leq$ 2. TURBT is not considered a major surgical procedure.

i. Patients must not have received treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 14 days prior to randomization. Exceptions:

- Patients may have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea).
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Physiological doses equivalent of 10 mg prednisone daily are allowed. Short term steroids given as antiemetic therapy, e.g. 4 mg dexamethasone or equivalent once a week, is allowed.

j. Patients must not have received a live, attenuated vaccine within 4 weeks prior to randomization or anticipate that such a live, attenuated vaccine will be required while on protocol treatment and up to 5 months after the last dose of protocol treatment.

- Inactivated influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 4 weeks prior to randomization or while on protocol treatment and up to 5 months after the last dose of protocol treatment.

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

5.5 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patient may or may not be radical cystectomy candidates.

c. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500/microliter (mcL); platelets ≥ 100,000/mcL; Hemoglobin ≥ 9 g/dL. These results must be obtained within 28 days prior to randomization.

d. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except patients with Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL), and AST or ALT < 2.5 x IULN. These results must be obtained within 28 days prior to randomization.

e. Patients must not have clinically significant liver disease that precludes patient from treatment regimens prescribed on the study (including, but not limited to, active viral, alcoholic or other autoimmune hepatitis, cirrhosis or inherited liver disease).

f. Patients must have adequate renal function as evidenced by calculated creatinine clearance ≥ 25 mL/min. The creatinine used to calculate the clearance result must have been obtained within 28 days prior to randomization. Actual body weight, not ideal body weight, must be used in the calculation.

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

g. Patients must have Zubrod Performance Status ≤ 2 (see Section 10.3).

h. Patients must have a baseline ECG performed within 30 days prior to randomization.

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

j. Patients must not have an active infection requiring oral or IV antibiotics within 14 days prior to randomization. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are not eligible. If patient develops urinary tract infection after TURBT they must have recovered from the infection prior to registration.

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

l. Patient must not have a history of active tuberculosis.

m. If patient has a known history of HBV or HCV, they must meet the following criteria within 28 days prior to randomization.

- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

n. Patients who are known to be positive for HIV are eligible only if they have all of the following:

d. Patients must have adequate hepatic function as evidenced by the following: total
- No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
- A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests within 28 days prior to randomization.

o. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for two years. Patients with localized prostate cancer who are being followed by an active surveillance program are also eligible.

p. Female patients of childbearing potential must have a serum pregnancy test prior to randomization. Patients must not be pregnant or nursing due to the potential teratogenic side effects of the protocol treatment. 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 protocol treatment, and for 5 months (150 days) after the last dose of all study drugs. A woman is considered to be of “reproductive potential” if she has had a menses at any time in the preceding 12 consecutive months.

q. Patients must not be known to be allergic to Chinese hamster egg or ovary cell products and must not have any known major allergic reactions to any study drug.

5.6 Specimen Submission Criteria

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

5.7 Quality of Life Criteria

a. Patients who can complete Patient-Reported Outcome instruments in English or Spanish must agree to complete the EORTC QLQ-C30, the EORTC QLQ-BLM30, the EPIC-26 (bowel domain only), and the EQ-5D-5L per protocol schedule of assessment.

5.8 Regulatory Criteria

a. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.