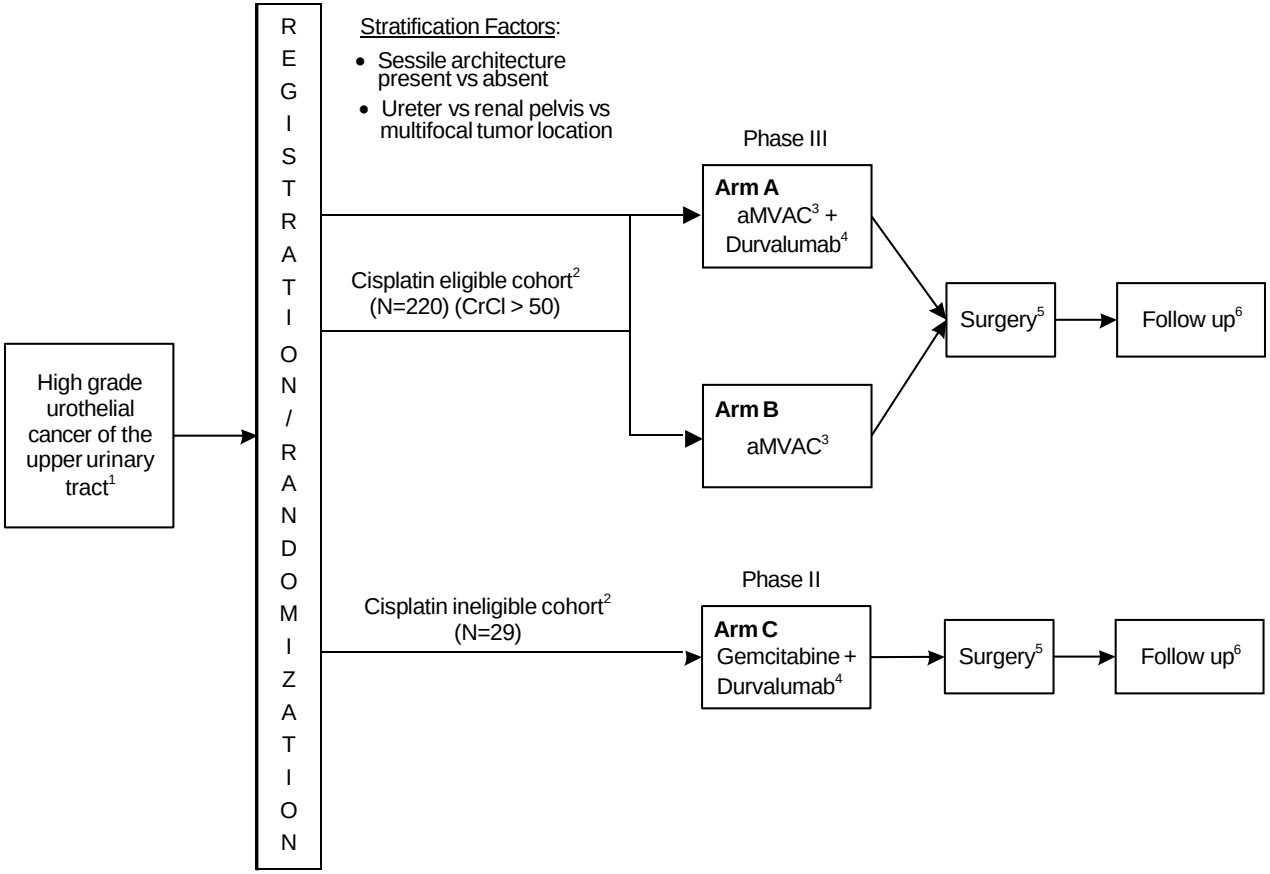
Schema



1. SOC biopsy and upper urinary tract mass on cross sectional imaging or directly visualized during upper tract endoscopy.
2. Cisplatin-Eligible (CrCl > 50) will be randomized between Arms A and B; Cisplatin-Ineligible (CrCl >15 & ≤50, hearing loss grade ≥3, neuropathy grade ≥2, and/or ECOG PS=2) will be assigned to Arm C. See Section 3.2 for full eligibility criteria.
3. aMVAC = accelerated methotrexate, vinblastine, doxorubicin and cisplatin with pegfilgrastim for 4 cycles; each cycle is 14 days.
4. Durvalumab: 1500 mg IV every 28 days in Arm A, 1500 mg IV every 21 days in Arm C.
5. Surgery = Radical nephroureterectomy and lymph node dissection (RNU).
6. Follow up every 3-6 months for 5 years after surgery.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

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 four weeks (28 days) later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria – Step 1 Registration and Randomization

_____3.1.1 Patient must be ≥18 years of age.

_____3.1.2 Patient must have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

_____ 3.1.3 Patient must have a diagnosis of high grade upper tract urothelial carcinoma proven by biopsy within 60 days prior to registration with one of the following:

- Upper urinary tract mass on cross-sectional imaging or
- Tumor directly visualized during upper urinary tract endoscopy before referral to medical oncology.

NOTE: Biopsy is SOC and required for enrollment to study. This is vital for best practice.

_____3.1.4 Patients must not have any component of small cell carcinoma. Other variant histologic types are permitted provided the predominant (≥ 50%) subtype is urothelial carcinoma.

_____3.1.5 Patient must have adequate organ and marrow function as defined below (these labs must be obtained ≤ 14 days prior to registration).

_____Leukocytes ≥ 3,000/mcL

Leukocytes:_____Date of Test:_____

_____Platelets ≥ 100,000/mcL

Platelets:_____Date of Test:_____

Total bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) (or ≤ 2.5 × ULN for patients with Gilbert's disease)

Total bilirubin:_____l ULN:_____

Date of Test:_____

Gilbert's disease?_____(Yes or No)

_____AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN

AST:_____ULN:_____Date of Test:_____

ALT:_____ULN:_____Date of Test:_____

Hgb ≥ 9 g/dL

Hgb:_____Date of Test:_____

NOTE: Packed red blood transfusion is allowed to achieve this parameter as per treating investigator.

_____3.1.6 Patients must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All patients of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.

A patient of childbearing potential is defined as any patient, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of childbearing potential?_____(Yes or No)

Date of blood test or urine study: _____

_____ 3.1.7 Patients of childbearing potential and sexually active patients must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse from the time of registration, while on study treatment and for at least 6 months after the last dose of protocol treatment.

_____3.1.8 Patient must have no evidence of metastatic disease or clinically enlarged lymph nodes (≥1.0 cm short axis) on imaging required within 28 days prior to registration (solitary slightly enlarged lymph node with negative biopsy is allowed).

NOTE: Patients with elevated alkaline phosphatase, calcium or suspicious bone pain/tenderness should also undergo baseline bone scans to evaluate for bone metastasis.

_____3.1.9 Patient must not have another active (or within 2 years) second malignancy other than resected non-melanoma skin cancers, resected in situ breast, cervical or other in situ carcinoma, and either clinically insignificant per the investigator (e.g. ≤Gleason 3+4) on surveillance or previously treated prostate cancer with no rising PSA and no plan to treat.

NOTE: Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial. Patients in whom concomitant or prior bladder/urethra predominant (≥50%) urothelial carcinoma have been surgically resected and demonstrated to be only non-invasive cancer (< cT1N0) are eligible regardless of time elapsed.

_____ 3.1.10 Patient must not have any uncontrolled illness including, but not limited to, ongoing or active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), symptomatic congestive heart failure (CHF), myocardial infarction (MI) in last 3 months, or unstable angina pectoris, significant uncontrolled cardiac arrhythmia, liver cirrhosis, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirements.

_____3.1.11 Patient must not have received prior radiation therapy to ≥ 25% of the bone marrow for other diseases.

_____ 3.1.12 Patient must not have received prior systemic anthracycline therapy.

NOTE: Patients who have received prior intravesical chemotherapy at any time for non-muscle invasive urothelial carcinoma of the bladder are eligible.

_____3.1.13 Patient must not have an active autoimmune disease requiring immunosuppressive therapy within 2 years prior to registration or a history of inflammatory bowel disease (IBD, colitis, or Crohn's disease), systemic lupus erythematosus, Sarcoidosis syndrome, Wegener syndrome or immune-related pneumonitis or interstitial lung disease. Patients with well-controlled hyper/hypothyroidism, celiac controlled by diet alone, diverticulosis, diabetes mellitus type I, vitiligo, alopecia, psoriasis, eczema, lichen planus, or similar skin/mucosa condition are eligible.

_____3.1.14 Patient must not be on or have used immunosuppressive medication within 14 days prior to the first dose of MEDI4736 (MEDI4736 (durvalumab)). The following are exceptions to this criterion:

- Intranasal, inhaled, intra-auricular, topical steroids, or local steroid injections (e.g. intra-articular injection).

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent at the time of enrollment.
- Steroids as premedications for hypersensitivity reactions (e.g. CT scan premedication).

_____3.1.15 Patient must not have a concomitant primary urothelial carcinoma of the bladder and/or urethra.

NOTE: Patients in whom concomitant or prior bladder/urethra predominant (≥50%) urothelial carcinoma have been surgically resected and demonstrated to be only non-invasive cancer (<cT1N0) are eligible regardless of time elapsed.

_____3.1.16 Patient must not have prior history of muscle-invasive urothelial carcinoma with or without systemic chemotherapy (T2-4a and/or N1) within 2 years prior to registration.

NOTE: Patients who have no evidence of disease (NED) for more than 2 years from the latest therapy (surgery, radiation, chemotherapy, or clinical trial) are eligible.

_____3.1.17 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

NOTE: These patients must be stable on their anti-retroviral regimen with evidence of at least two undetectable viral loads within the past 6 months on the same regimen; the most recent undetectable viral load must be within the past 12 weeks. They must have a CD4 count of greater than 250 cells/mcL over the past 6 months on this same anti-retroviral regimen and must not have had a CD4 count <200 cells/mcL over the past 2 years, unless it was deemed related to the cancer and/or chemotherapy induced bone marrow suppression. They must not be currently receiving prophylactic therapy for an opportunistic infection and must not have had an opportunistic infection within the past 6 months.

NOTE: For patients who have received chemotherapy in the past 6 months, a CD4 count <250 cells/mcL during chemotherapy is permitted as long as viral loads were undetectable during this same chemotherapy. They must have an undetectable viral load and a CD4 count ≥250 cells/mcL within 7 days of registration.

_____ 3.1.18 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

NOTE: Testing for HIV, Hepatitis B or Hepatitis C is not required unless clinically indicated.

_____3.1.19 Patients with a history of hepatitis C virus (HCV) infection must have been treated and have undetectable viral load. For patients with HCV

infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____3.1.20 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

_____3.1.21 Patient must not have received live attenuated vaccine within 30 days prior to the first dose of MEDI4736 (durvalumab), while on protocol treatment and within 30 days after the last dose of MEDI4736 (durvalumab).

_____ 3.1.22 Patient must not have had a major surgical procedure (as defined by the Investigator) within 28 days prior to registration.

_____ 3.1.23 Patient must not have a history of allogenic organ transplantation.

_____ 3.1.24 Patient must have a body weight of > 30 kg.

_____ 3.1.25 Patient must have a life expectancy of ≥ 12 weeks.

_____ 3.1.26 Patient must have a creatinine clearance > 15 ml/min as by Cockroft-Gault or 24-hour creatinine clearance within 28 days prior to registration.

Creatinine clearance_____Date of Test_____

NOTE: Patients will be assigned to cisplatin-ineligible and cisplatin-eligible cohorts based on their creatinine clearance, ECOG performance status, and grade (if any) of peripheral neuropathy and hearing loss in keeping with SOC cisplatin contraindications. Patients that are cisplatin-eligible will be randomized to either Arm A or Arm B.

3.1.26.1 Patients that meet the following criteria will be assigned to the cisplatin-ineligible Arm C:

_____3.1.26.1.1 Creatinine clearance of >15 ml/min and ≤50 ml/min.

_____3.1.26.1.2 Patient must have an absolute neutrophil count (ANC)) ≥ 1,000/mcL obtained ≤ 14 days prior to registration.

ANC:_____Date of Test:_____

_____ 3.1.26.1.3 Patient must have ECOG Performance Status 0-2.

3.1.26.2 Patients that meet the following criteria will be randomized to cisplatin-eligible Arm A or Arm B:

_____3.1.26.2.1 Patient must have an absolute neutrophil count (ANC) ≥ 1,500/mcL obtained ≤ 14 days prior to randomization.

ANC:_____Date of Test:_____

_____	3.1.26.2.2	Patient must have ECOG Performance Status 0-1.
_____	3.1.26.2.3	Patient must have left ventricular ejection fraction (LVEF) ≥ 50% by (either MUGA or 2-D echocardiogram) obtained within 28 days prior to randomization.
_____	3.1.26.2.4	Patient must not have peripheral neuropathy ≥ Grade 2 or hearing loss ≥ Grade 3.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.