Version 05/17/24 (Add. #2)

NCI National Clinical Trials Network

EA8192

ECOG-ACRIN cancer research group

For Patients with Urothelial Cancer

EA8192 Available Through ECOG-ACRIN Cancer Research Group

Phase II/III Trial of Durvalumab and Chemotherapy for Patients with High Grade Upper Tract Urothelial Cancer Prior to Nephroureterectomy

Patient Population

See Section 3 for Complete Eligibility Details

- Age ≥ 18 years, adequate lab values, body weight of > 30 kg, life expectancy of ≥ 12 weeks
  - ◊ *Note: Patients will be assigned to cisplatin-ineligible/ eligible cohorts based on their creatinine clearance, ECOG PS and grade (if any of peripheral neuropathy and/or hearing loss. Cisplatin-eligible patients will be randomized to Arm A or B*
- Must have diagnosis of high grade upper tract urothelial carcinoma proven by biopsy within 84 days prior to registration/randomization with either:
  - ◊ Upper urinary tract mass on cross-sectional imaging
  - ◊ Tumor directly visualized during upper urinary tract endoscopy before referral to medical oncology
- Must not have any component of small cell/ neuroendocrine carcinoma (see protocol for details)
- No evidence of metastatic disease or clinically enlarged regional lymph nodes on imaging required within 28 days prior to registration (see protocol for details)
- Must meet criteria per protocol for malignancy history
- Must not have any uncontrolled illness per protocol
- Must not have received prior radiation therapy to ≥ 25% of the bone marrow for other diseases, or prior systemic anthracycline therapy
- Must not have history of/active autoimmune disease requiring immunosuppressive therapy within 2 years prior to registration/randomization, or any history of inflammatory bowel disease, neuromuscular autoimmune condition, or immune-related pneumonitis or interstitial lung disease (see protocol)
- No immune suppressive medication within 14 days of the first dose of durvalumab (exceptions per protocol)
- NYHA class 2B or better (if cardiac history/symptoms)
- No major surgery within 28 days of registration/ randomization
- No history of allogeneic organ transplantation

Treatment Plan

See Section 5 for Complete Treatment Details

Patients are assigned to a treatment arm based on their baseline renal function; i.e., patients eligible for cisplatin (creatinine clearance > 50 ml/min) will be randomized to Arm A or B/ patients ineligible for cisplatin (creatinine clearance > 15 and ≤ 50 ml/min) will be on Arm C

1 cycle = 14 days; repeat for 4 cycles

- **Arm A**– neoadjuvant aMVAC + durvalumab (1500 mg IV over 60 mins, day 1 every other cycle) prior to radial nephroureterectomy with template lymph node dissection (RNU)
- **Arm B**– neoadjuvant aMVAC prior to radical nephroureterectomy with template lymph node dissection (RNU)
- *NOTE:*
  - ◊ *Dosing is based on actual body weight*
  - ◊ *Cisplatin can be 70 mg/m² over 1-2 hours or 35 mg/m² on days 1 and 2*
  - ◊ *aMVAC is administered per institutional standard; time window is –2/+4 days*

1 cycle = 21 days; repeat for 4 cycles

- **Arm C**- neoadjuvant durvalumab (1500 mg) + Gemcitabine (1000 mg/m² IV over 30 mins days 1 and 8) prior to radical nephroureterectomy with template lymph node dissection (RNU)

Surgery details (identical on all arms)- patients with continued lack of radiographic presence of metastatic or unresectable disease following neoadjuvant chemotherapy will proceed to nephroureterectomy and lymph node dissection

- Surgery must take place 21-60 days from the last dose of neoadjuvant systemic therapy
- The surgical approach is left at the surgeon's discretion as long as protocol criteria are met

Study Chair:
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Patient Enrollment

All Sites: Oncology Patient Enrollment Network (OPEN) https://open.ctsu.org/open

Protocol Information

ECOG-ACRIN Operations-Boston: 857-504-2900, http://ecog-acrin.org (Member Login)

Please Enroll Your Eligible Patients!

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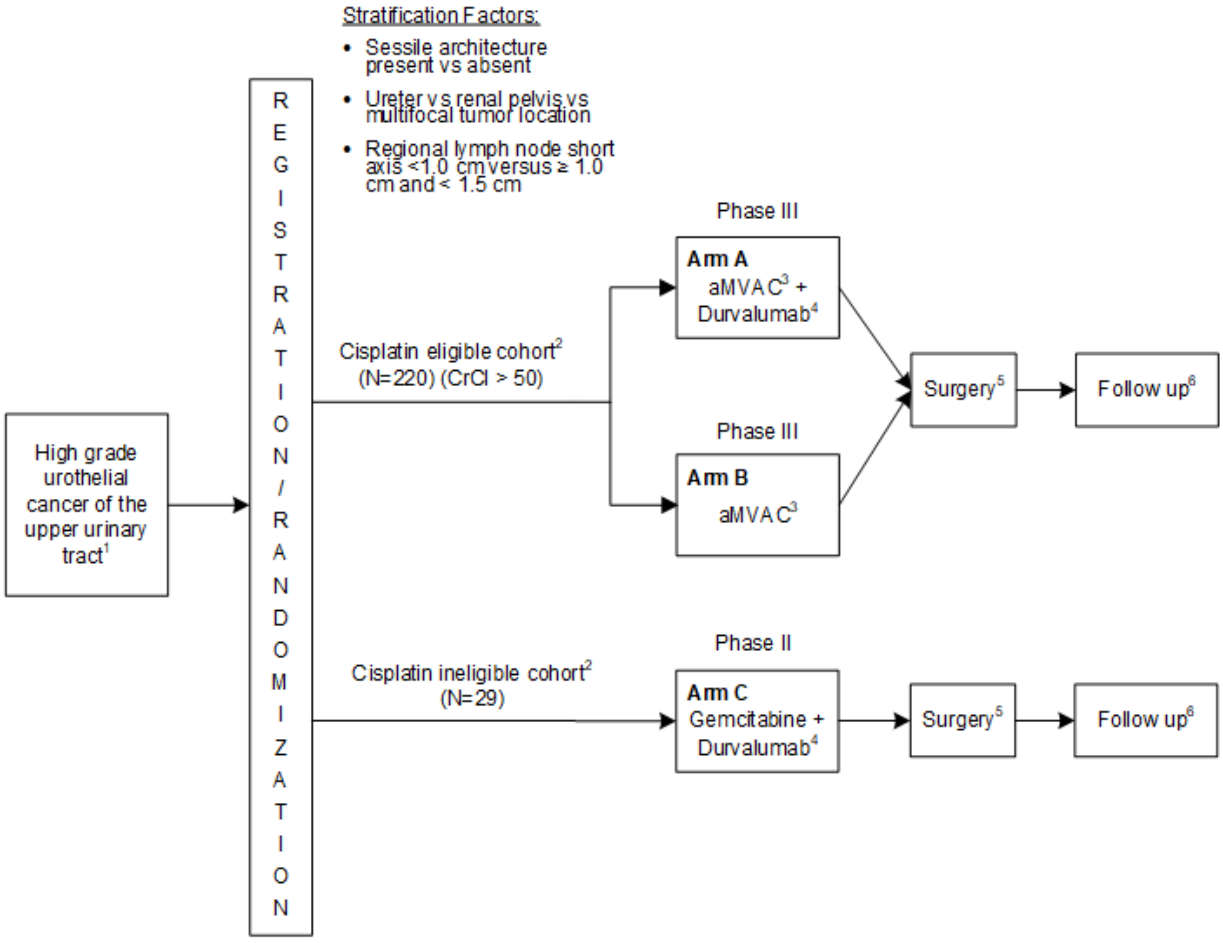
Schema



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.