v.06/22/26 (Add. #5)

NCI National Clinical Trials Network

EA8192

ECOG-ACRIN cancer research group

For Patients with Urothelial Cancer

Please Enroll Your Eligible Patients!

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 protocol Section 3 for complete eligibility criteria

- Age ≥ 18 years; adequate lab values; body weight > 30 kg; life expectancy ≥ 12 weeks
  - ◊ *Note: Patients are assigned to cohorts based on their creatinine clearance, ECOG PS and grade (if any) of peripheral neuropathy and/or hearing loss*
- Must have diagnosis of high grade upper tract urothelial carcinoma (UC) expected within 14 weeks (98 days) prior to registration/randomization with either:
  - ◊ Biopsy (preferred) and either upper urinary tract mass on cross-sectional imaging or tumor directly visualized during upper urinary tract endoscopy
  - ◊ High grade cytology and clinically estimated invasive upper urinary tract mass on cross-sectional imaging or tumor directly visualized during upper urinary tract endoscopy
- Must not have any component of small cell/ neuroendocrine carcinoma (see criterion 3.1.4)
- No evidence of metastatic disease or clinically enlarged regional lymph nodes on imaging required within 28 days prior to registration (see criterion 3.1.8)
- Must meet criteria per 3.1.9 for malignancy history; no history of ≥ pT4b, N+, and/or M1 UC
- Must not have any uncontrolled illness per protocol
- No prior RT to ≥ 25% of the bone marrow for other diseases, or prior systemic anthracycline therapy
- No 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 (with exceptions per 3.1.13)
- No immunosuppressive medication within 14 days prior to first dose of durvalumab (exceptions per 3.1.14)
- NYHA class 2B or better (if cardiac history/symptoms)
- No history of allogeneic organ transplantation
- No major surgical procedure within 28 days of registration

Treatment Plan

See protocol Section 5 for complete treatment details

Treatment should start within 7 days after Step 1 registration/randomization

Patients eligible for cisplatin are randomized to:

- **Arm A** *(cycle = 14 days; repeat for 4 cycles)*
  - ◊ Neoadjuvant aMVAC on Day 1 (–2/+4 days) every cycle, administered per institutional standards
  - ◊ Durvalumab 1500 mg IV over 60 mins, Day 1 of every other cycle (i.e., Cycles 1 and 3)
  - ◊ G-CSF (agent per investigator discretion)
- **Arm B** *(cycle = 14 days; repeat for 4 cycles)*
  - ◊ Neoadjuvant aMVAC (same as Arm A)
  - ◊ G-CSF (agent per investigator discretion)

Arms A/B Notes: See Sections 5.1.1-2 for aMVAC and G-CSF dosing recommendations; C1D1 weight may be used for all cycles; cisplatin dosing may be split over Days 1 and 2

Patients ineligible for cisplatin were registered to CLOSED- Arm C *(cycle = 21 days; repeat for 4 cycles)*

- Durvalumab 1500 mg over 60 mins on Day 1
- Gemcitabine 1000 mg/m² IV over 30 mins on Days 1 and 8

Surgery (identical on all arms): patients with continued lack of radiographic presence of metastatic or unresectable disease following neoadjuvant chemotherapy will proceed to nephroureterectomy and template 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
- Primary tumor, normal kidney/ureter tissue, and regional lymph nodes will be harvested at surgery

Study Chair:
Jean Hoffman-Censits, MD

Study Co-Chairs:
Petros Grivas, MD, PhD, FASCO
Vitaly Margulis, MD

NCTN Champions:
•***SWOG:*** Sarah Psutka, MD, MSc; Abhishek Tripathi, MD

Patient Enrollment (Oncology Patient Enrollment Network [OPEN])

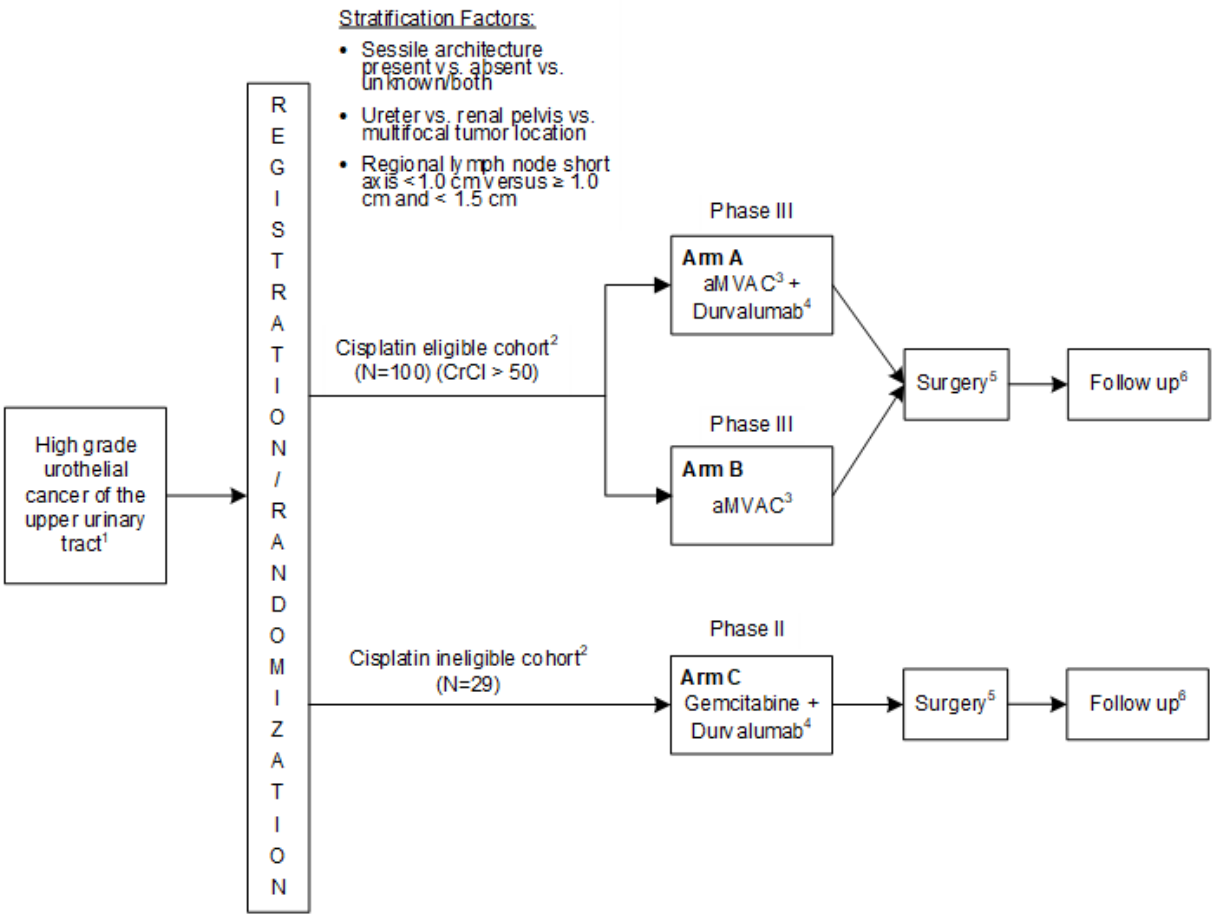
https://open.ctsu.org/open 1-888-823-5923

Protocol Information (ECOG-ACRIN Operations – Boston)

http://ecog-acrin.org (Member Login) 1-857-504-2900

EA8192

Schema



1. Diagnosis proven via biopsy or high-grade cytology with an upper urinary tract mass on cross-sectional imaging or a mass directly visualized during upper tract endoscopy. See Section 3.1.3 for additional details.
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 3.1 for full eligibility criteria.
3. aMVAC = accelerated methotrexate, vinblastine, doxorubicin and cisplatin with G-CSF 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.