Version 05/26/23 (Add. #6)

NCI National Clinical Trials Network

EA8185/INSPIRE

For Patients with Bladder Cancer

EA8185 Available Through ECOG-ACRIN Cancer Research Group

Phase II Study of Bladder-Sparing Chemoradiation with Durvalumab in Clinical Stage III, Node Positive Bladder Cancer (**INSPIRE**)

Patient Population

See Section 3.0 for Complete Eligibility Details

Step 1 (Randomization) Eligibility Criteria:

- Age ≥ 18 years, ECOG PS 0-2, adequate lab values
- Histologically proven pure or mixed urothelial cancer of the bladder (small cell carcinoma is excluded, however other variant histologies are permitted provided a component of urothelial carcinoma is present)
- Must have documented node-positive and non-metastatic disease (any T, any N, M0), defined per protocol prior to receiving systemic/induction chemotherapy
- See protocol for disease assessment requirements (criteria for patients that *have* or *have not* completed induction [systemic] chemo prior to enrollment)
- No previous RT to the pelvic area
- No presence of concomitant active upper tract/urethra tumors; see protocol regarding previously treated cancers
- Immune checkpoint inhibitors for non-muscle invasive disease are permitted > 12 months prior to Step 1 randomization
- Must not have history of prior documented autoimmune disease within 2 years of Step 1 randomization (see protocol)
- No active infection (see protocol for details)
- Must not have clinically significant liver disease that precludes patient from study treatment
- Patients with known history/current symptoms of cardiac disease/history of treatment with cardiotoxic agents should be NYHA class IIB or better

Step 2 (Registration) Eligibility Criteria:

- No progression (imaging and cystoscopy with biopsy confirmation, per protocol); no T2 disease in the bladder
- See protocol for chemoRT + durvalumab (Arm C) requirements
- Patients on Arm D (chemoRT) must have achieved either complete clinical response OR have demonstrated clinical benefit prior to going to observation (Arm F)

Treatment Plan

See Section 5.0 for Complete Treatment Details

Add#4 removed the requirement for induction chemo prior to randomization to ChemoRT +/- durvalumab (i.e., Arms A and B were removed from the protocol)

Step 1 (randomization; concurrent ChemoRT +/- durvalumab):

- **Arm C**– durvalumab IV every 21 days for 3 doses along with physician's choice for concurrent chemotherapy (per protocol)
- **Arm D**– chemoRT; physician's choice per protocol

Step 2 (registration; adjuvant durvalumab vs observation):

- Patients will be evaluated for clinical response 8 weeks (+/- 2 weeks) post completion of concurrent chemoRT +/- durvalumab; patients will undergo CT chest, abdomen and pelvis
- Response to bladder will be documented by cystoscopy and biopsy of the previous tumor affected sites +/- random biopsies per protocol
- Patients on Arm C with clinical CR/clinical benefit will go to **Arm E**– adjuvant durvalumab (once every 28 days, 6 doses/cycles)
- Patients on Arm D who achieve clinical CR/clinical benefit will go to **Arm F**– observation
- Patients previously on Arm C or D who do NOT achieve clinical CR/benefit will be considered for salvage cystectomy if possible

Notes:

- *Chemotherapy (and durvalumab) to start 4 days (before or after) the start of radiation therapy*
- *A Pre-Treatment RT review is required for the first case registered at a site- this will take up to 3 business days; the deadline of starting radiation is within 20 business days of Step 1 randomization*
- *Pre-medication for chemotherapy is based on institutional practices*
- *Radiotherapy should be delivered over 6.5-8 weeks*

Study Chair (EA):
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Co-Chair (NRG):
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EA8185 represents a joint scientific collaboration between EA and NRG, with EA as the lead group for trial conduct.

Patient Enrollment

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

Protocol Information

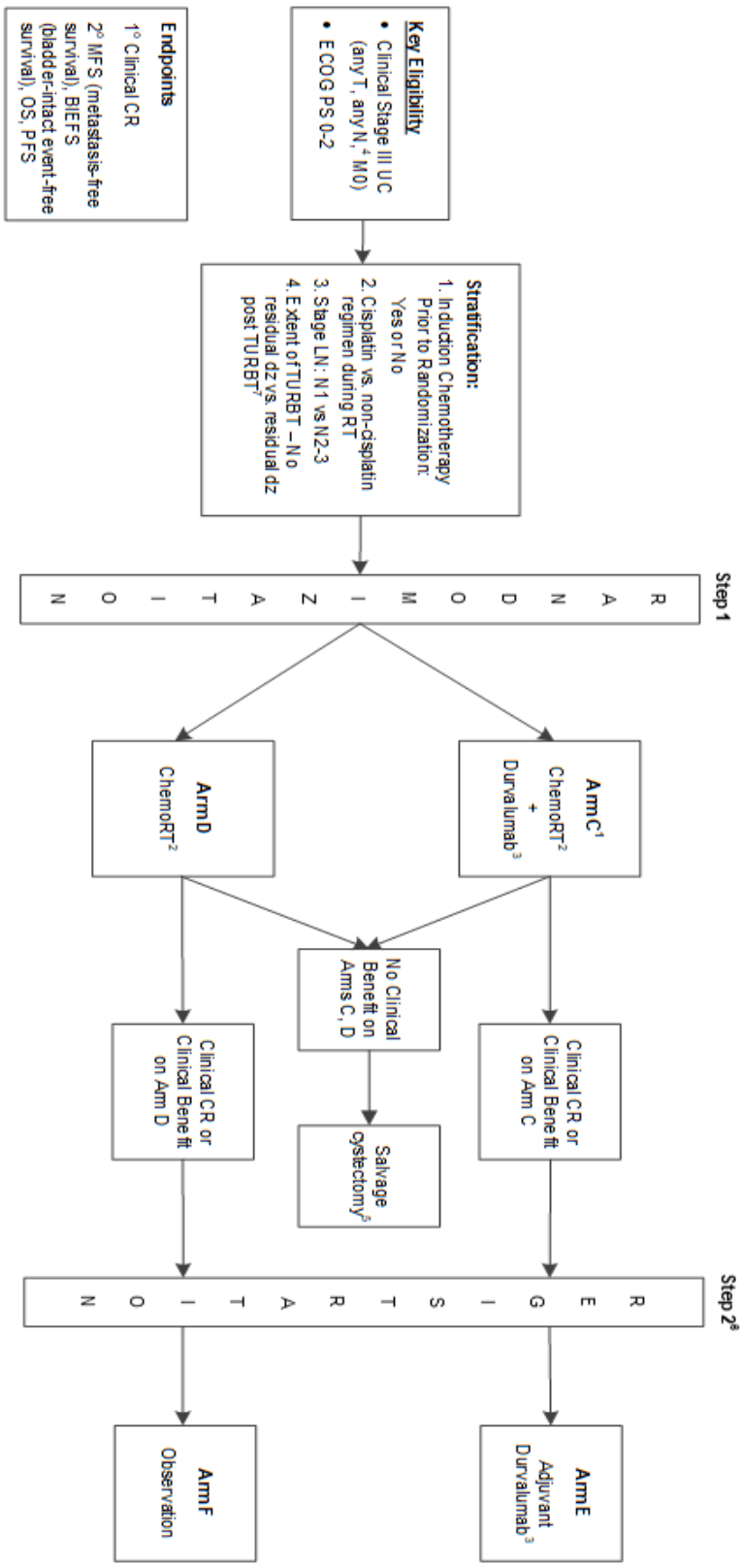
ECOG-ACRIN Operations-Boston: 857-504-2900, http://ecog-acrin.org (Member Login)

Please Enroll Your Eligible Patients!

EA8185

ECOG-ACRIN cancer research group

Schema



1. 1st 6 patients randomized to Arm C (ChemoRT + Durvalumab) will be evaluated for safety run.
2. Chemosensitizing options: (weekly Cisplatin or 5-FU+MMC, or twice weekly Gemcitabine) +EBRT. See Section 5.1 for treatment options and descriptions.
3. Durvalumab will be given Q3 weekly x 3 doses on Arm C and it will be given Q4 weekly x 6 doses on Arm E.
4. Node positivity must have been defined prior to using any systemic chemotherapy or induction chemotherapy.
5. Salvage cystectomy when possible.
6. Restaging 8 weeks (+/-2 weeks) with imaging and cystoscopy and biopsy.
7. TURBT: trans-urethral resection of bladder tumor.

NOTE: Arms A and B removed in Addendum 4.