A Phase II Trial of Risk Enabled Therapy After Initiating Neoadjuvant Chemotherapy for Bladder Cancer (RETAIN BLADDER)  
NCT02710734

BACKGROUND
- Cisplatin-based neoadjuvant chemotherapy followed by cystectomy or chemoradiation is the standard of care for urothelial carcinoma patients with muscle invasive bladder cancer.
- Both cystectomy and chemoradiation carry potential short- and long-term toxicity and quality of life implications.
- Recent work has shown that mutational status in DNA damage repair/response genes are predictive of pathologic response to neoadjuvant chemotherapy at the time of cystectomy, with those patients achieving pT0 disease demonstrating excellent long-term survival.
- Sparing patients cystectomy or chemoradiation after neoadjuvant chemotherapy without compromising oncologic outcomes would improve quality of life and decrease morbidity.

OBJECTIVES
- **Primary Aim:** To evaluate a risk-adapted approach to the treatment of muscle invasive bladder cancer.
- **Primary Objective:** To evaluate the metastasis-free survival at 2 years for all patients.
- **Key Secondary Objectives:**
  - To assess quality of life with neoadjuvant AMVAC and subsequent risk-adapted treatment of muscle invasive bladder cancer.
  - To assess the feasibility of an Endoscopic Tumor Quantification System.
  - To assess toxicity in each treatment arm.
  - To assess genomic correlates and mutations in urinary cell-free DNA.
  - To assess bladder preservation rates with neoadjuvant chemotherapy without compromising oncologic outcomes.
  - To assess the rate of any urothelial carcinoma recurrence and long-term survival.

**MAJOR INCLUSION CRITERIA**
- Primary urothelial or predominantly urothelial carcinoma of the bladder
- AJCC clinical stage T2-T3 N0M0 disease
- ECOG PS 0-1
- Adequate organ (CrCl ≥ 50 ml/min) and bone marrow function
- Left ventricular ejection fraction ≥ 50%
- No prior pelvic radiation
- No component of small cell histology
- No prior systemic therapy or radiation therapy for urothelial carcinoma
- Hydronephrosis that has not been adequately addressed/assessed
- Modern benchmark=MFS of 78%

**MAJOR EXCLUSION CRITERIA**
- Any component of small cell histology
- Prior pelvic radiation
- Prior systemic therapy or radiation therapy for urothelial carcinoma
- Hyponatremia that has not been adequately addressed/assessed

**STATISTICAL PLAN**
- Single arm, single-stage Phase II study
- Success/failure defined as nodal (>cN1), locally recurrent (>cT4a) or metastatic disease at 2 years
- Historical benchmark=MFS of 64%
- Modern benchmark=MFS of 78%
- Non-inferiority margin of 14%
- Null Hypothesis=success proportion (p) is ≤ 64%
- Non-inferiority margin of 14%
- Historical benchmark=MFS of 64%
- Modern benchmark=MFS of 78%
- Non-inferiority margin of 14%
- Null Hypothesis=success proportion (p) is ≤ 64%
- Non-inferiority margin of 14%
- Patient replaced if unable to sequence tissue
- Historical benchmark=MFS of 64%
- Modern benchmark=MFS of 78%
- Non-inferiority margin of 14%
- Null Hypothesis=success proportion (p) is ≤ 64%
- Non-inferiority margin of 14%

**MAJOR EXCLUSION CRITERIA**
- Any component of small cell histology
- Prior pelvic radiation
- Prior systemic therapy or radiation therapy for urothelial carcinoma
- Hyponatremia that has not been adequately addressed/assessed

**SEQUENCING & CORRELATIVE WORK**
- Next-generation sequencing (NGS) is performed by Caris Life Sciences on genomic DNA isolated from FFPE TURBT #1 tumor samples during the period patients are undergoing AMVAC using NextSeq platform (Illumina, Inc., San Diego, CA). No matched normal tissue is sequenced. A minimum of 95% of the tumor is sequenced to further validate and investigate biomarkers of response and outcomes to NAC.
- We hypothesize that (1) AMVAC followed by chemoradiation is particularly effective in a subgroup with the aforementioned molecular signature and (2) patients who have a complete response at the time of cystectomy or those who go on to active surveillance due to no visible disease and the presence of genomic alterations, will have detectable mutations in cellular-free DNA prior to NAC but will no longer have those mutations detectable after NAC.
- Tumor as well as urine and serum samples will be collected at all time points in the study to further validate and investigate biomarkers of response and outcomes to NAC.

**REFERENCES & ACKNOWLEDGMENTS**
4. Teo et al. CCR. 2017
7. Plimack E et al. JCO. 2014

This study is being supported by Fox Chase Cancer Center and Caris Life Sciences. We want to thank all the participating patients and their families.