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

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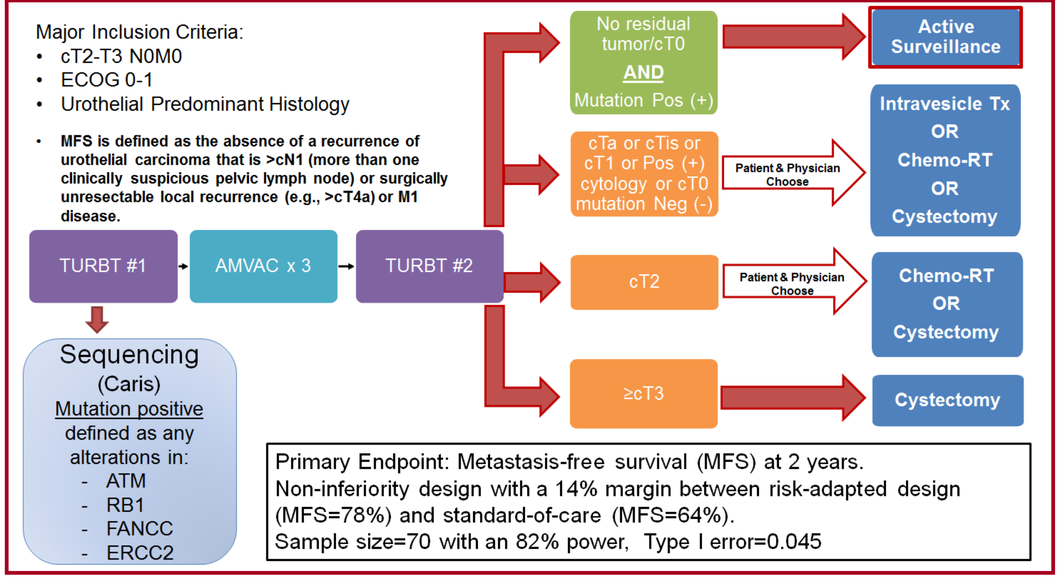
## BACKGROUND

- 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 mutations 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.[1-4]
- **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 the rate of any urothelial carcinoma recurrence in active surveillance patients
  - To assess bladder preservation rates with neoadjuvant AMVAC and subsequent risk-adapted treatment
  - To assess the feasibility of an Endoscopic Tumor Quantification System
  - To assess quality of life with neoadjuvant AMVAC and subsequent risk-adapted treatment (EORTC QLQ-BLM 30, SHIM, FSFI, AUA symptoms score)
  - To assess genomic correlates and mutations in urinary cell-free DNA.
  - To assess toxicity in each treatment arm

## CLINICAL TRIAL SCHEMA




Primary Endpoint: Metastasis-free survival (MFS) at 2 years.
Non-inferiority design with a 14% margin between risk-adapted design (MFS=78%) and standard-of-care (MFS=64%).
Sample size=70 with an 82% power, Type I error=0.045

## MAJOR INCLUSION CRITERIA

- Primary urothelial or predominantly urothelial carcinoma of the bladder
- AJCC clinical stage T2-T3 N0M0 disease
- ECOG PS 0-1
- Left ventricular ejection fraction ≥ 50%
- Adequate organ (CrCl ≥ 50 ml/min) and bone marrow function

## MAJOR EXCLUSION CRITERIA

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

## STATISTICAL PLAN

- Single arm, single-stage Phase II study
- Success=freedom from nodal (>cN1), locally advanced (>cT4a) or metastatic disease at 2 years
- Historical benchmark=MFS of 64%[5,6]
- Modern benchmark=MFS of 78%[7]
- Non-inferiority margin of 14%
- Null Hypothesis=success proportion (p) is ≤ 64% vs the alternative that p > 0.64.
- Reject null if lower limit of 95% CI is ≤ 64%
- N=70; Type I error = 4.5%; Power = 82%
- Patient replaced if unable to sequence tissue or <2 cycles of AMVAC delivered

## 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 custom-designed SureSelect XT assay is used to enrich 592 whole-gene targets (Agilent Technologies, Santa Clara, CA). All variants are detected with > 99% confidence based on allele frequency and amplicon coverage with an average sequencing depth of coverage of > 500 and with an analytic sensitivity of 5%. Tumor enrichment is achieved by harvesting targeted tissue by manual microdissection performed on all cases prior to molecular testing.
- Previously published data suggest that molecular alterations in DNA repair and chromatin maintenance genes *ATM*, *RB1* and *FANCC* as well as the nucleotide excision repair (NER) gene *ERCC2* predict response to cisplatin-based chemotherapy.
- 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 urinary cell-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.

## ACTIVE SURVEILLANCE SCHEDULE

| | Year 1 | Year 2 | Year 3 | Year 4-5 | Thereafter |
|---|---|---|---|---|---|
| H&P and Labs | Q3 months | Q4 months | Q4 months | Q6 months | Annually |
| Urine Cytology | Q3 months | Q4 months | Q4 months | Q6 months | Annually |
| Cystoscopy | Q3 months | Q4 months | Q4 months | Q6 months | Annually |
| Imaging | Q3 months | Q4 months | Q4 months | Annually | Annually |

## REFERENCES & ACKNOWLEDGMENTS

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