



Dan L Duncan Comprehensive Cancer Center

Clinical Applications for Liquid Biopsy in GU Cancers Update

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**Baylor St. Luke's
Medical Center**

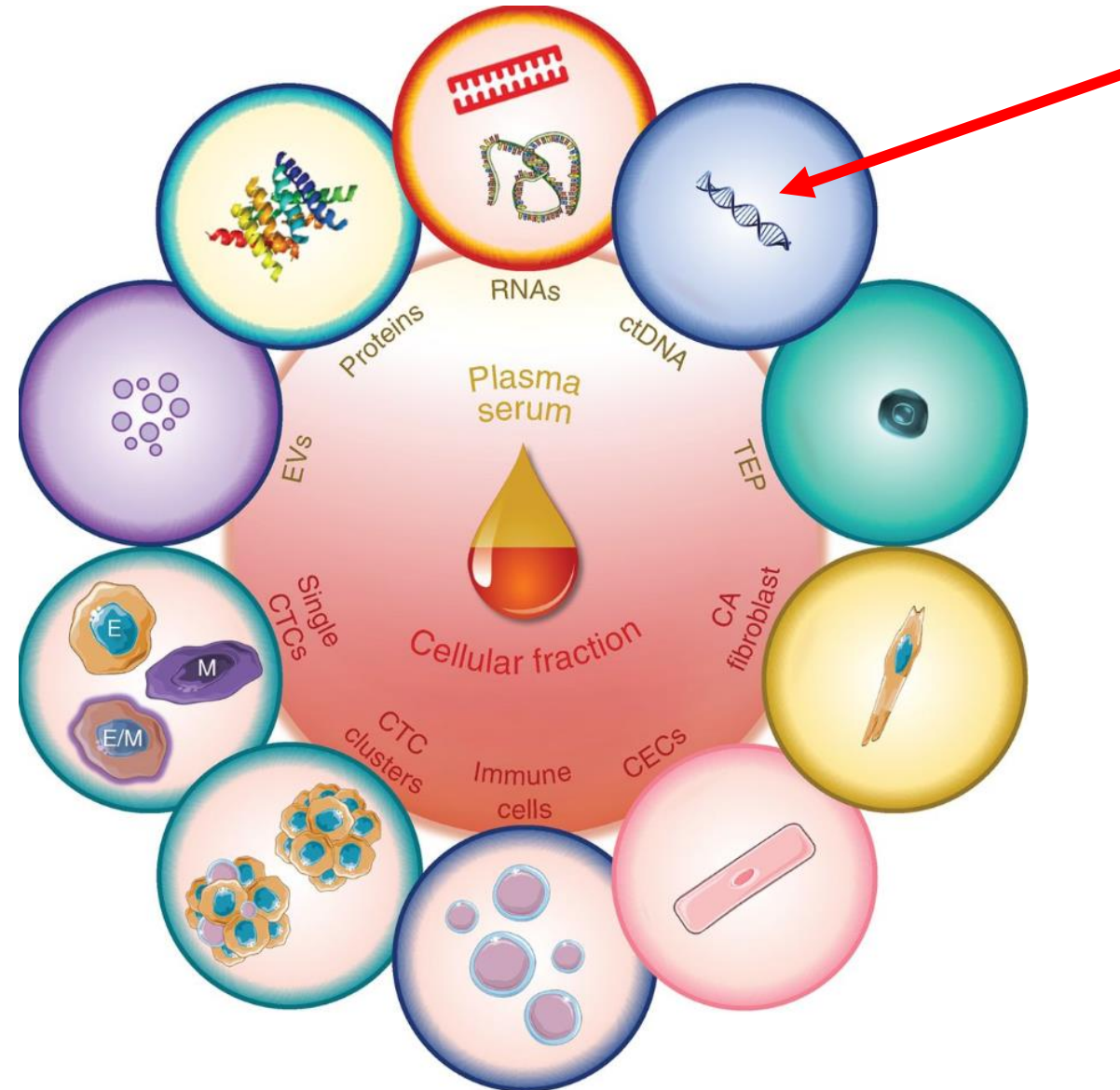
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Outline

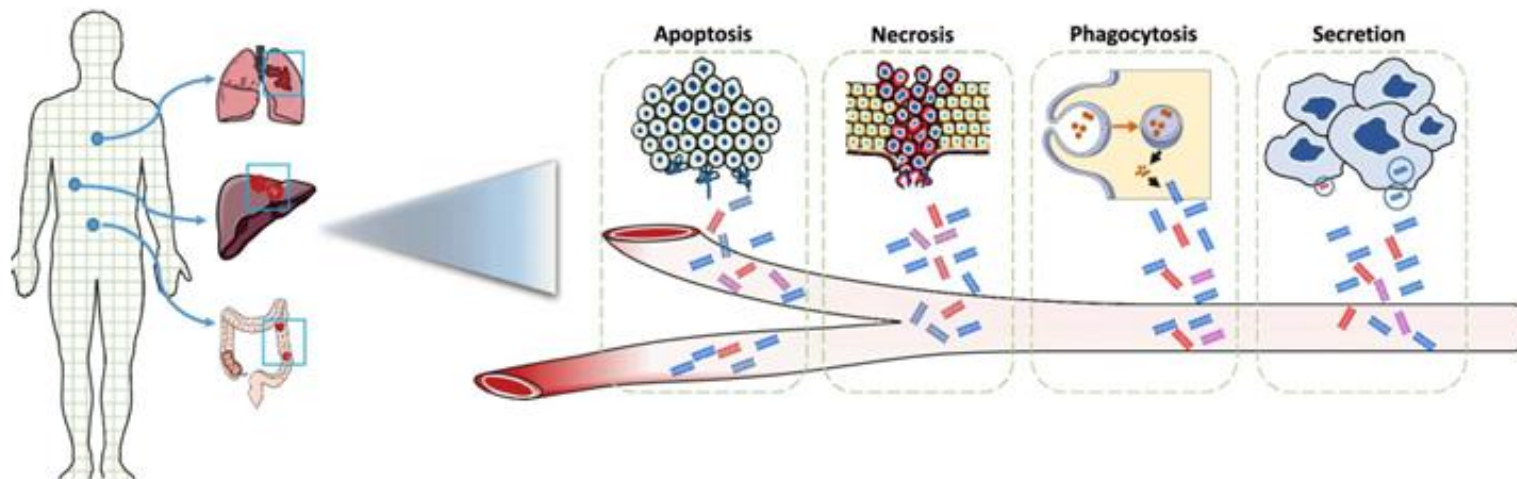
- Background
- Role of liquid biopsies in bladder cancer (NMIBC, MIBC, mUC)
- Role of liquid biopsies in prostate cancer
- Role of liquid biopsies in testicular cancer

The liquid biopsy



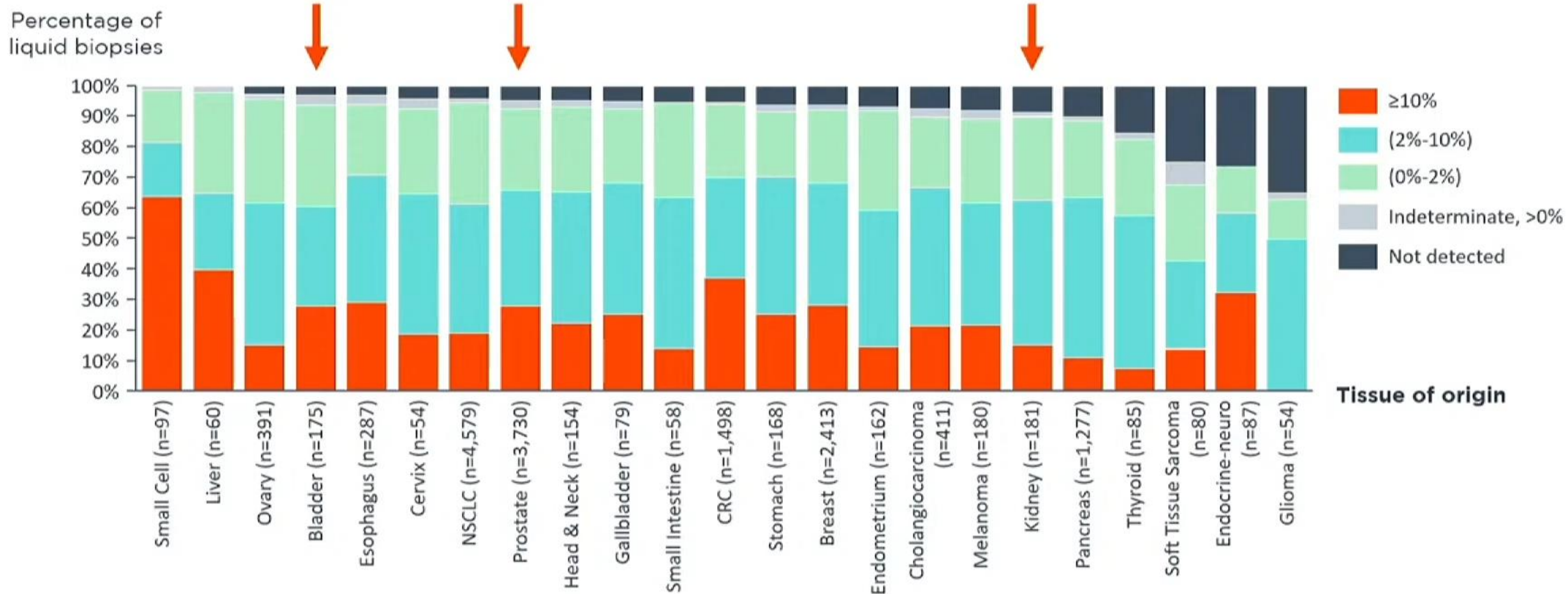
What is circulating tumor DNA?

- Short fragments (post-apoptotic) of tumor-derived DNA in the blood (or urine)
- Mixed with cell-free DNA from non-cancer cells
- “Real time” analysis: half-life of ctDNA in plasma ~2-3 hours
- Tumor informed vs tumor-agnostic assays



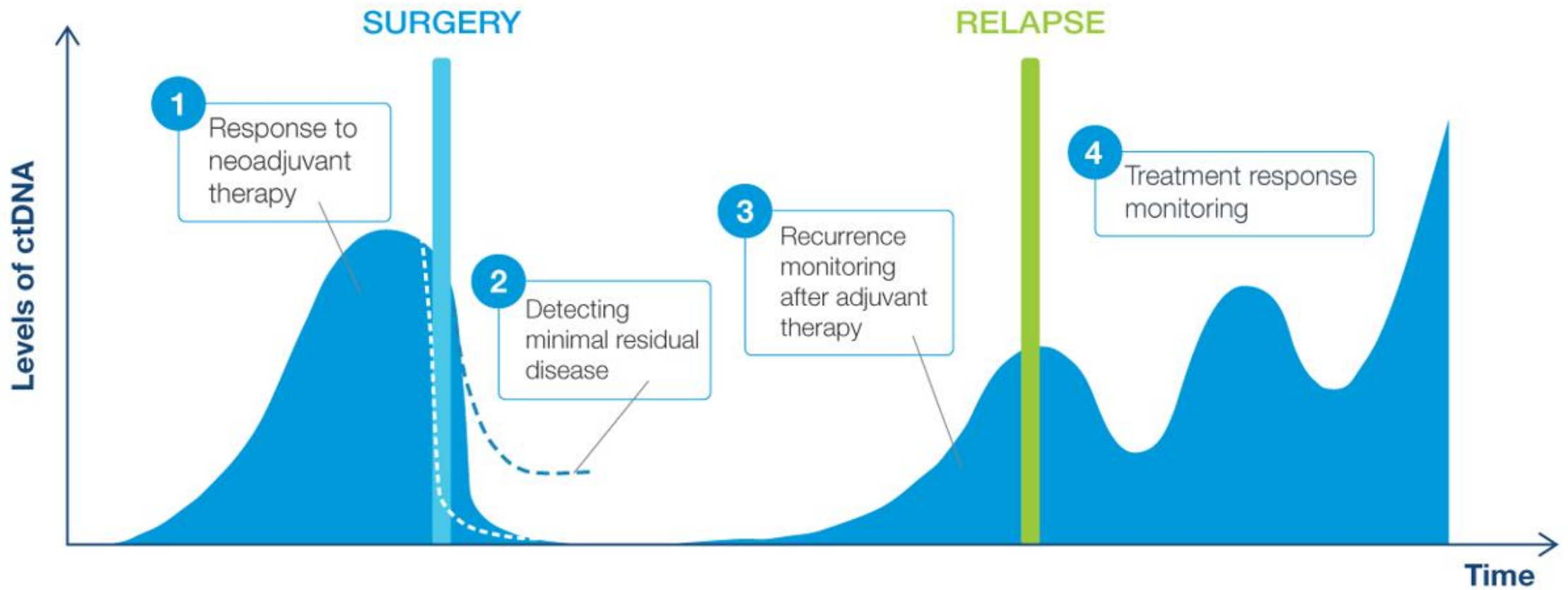
ctDNA is detectable but variable across tumor types

Tumor fraction estimation based on aneuploidy and variant information



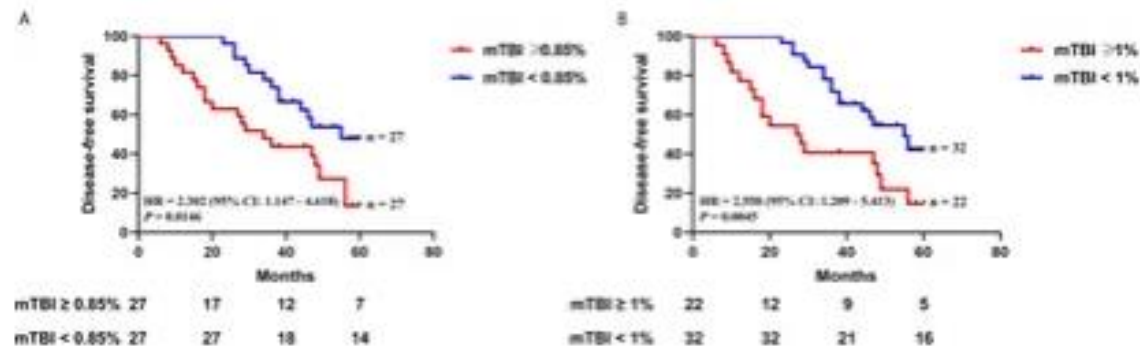
Therapeutic applications of ctDNA in management of GU cancers

- Curative Setting- Detection of MRD
 - Risk Stratification
 - HIGH RISK patients – Adjuvant treatment intensification?
 - LOW RISK patients- Do they need adjuvant therapy vs surveillance alone?
 - Better surveillance following curative therapies?
- Metastatic Setting – Monitoring dynamic changes in ctDNA and guiding treatment strategies to overcome therapeutic resistance
 - Treatment monitoring
 - Early identification of response to systemic treatments
 - Balance treatment response with associated toxicity
 - Complement radiographic findings in assessing treatment response
 - Personalizing further targeted treatments
 - Characterization and identification of clonal evolution driving treatment resistance



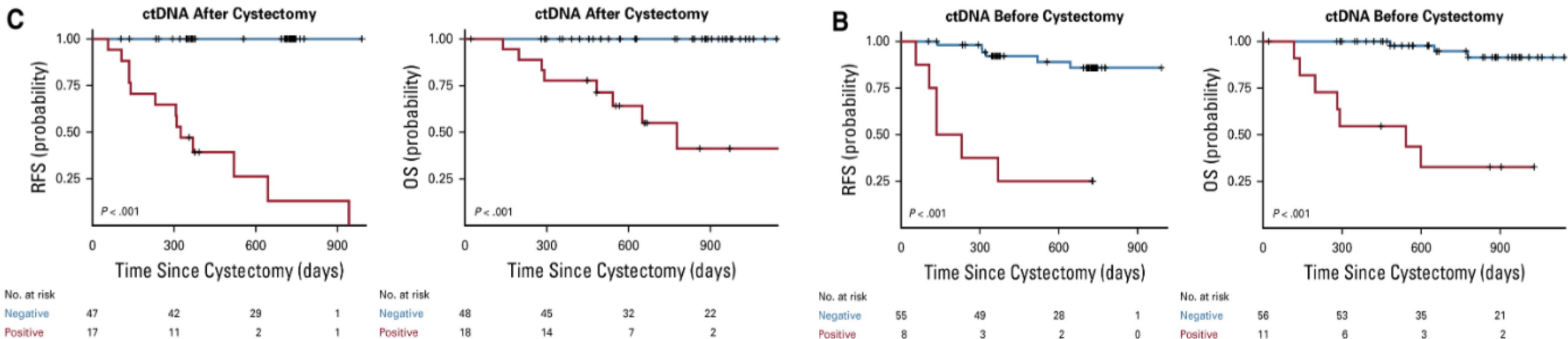
ctDNA in Non-Muscle Invasive Bladder Cancer

- Tumor related ctDNA detected in ~50% of patients
- High concordance of somatic alterations between tumor DNA and plasma ctDNA in patients with T1 disease and tumors >3cm
- Increased ctDNA burden associated with worse prognosis



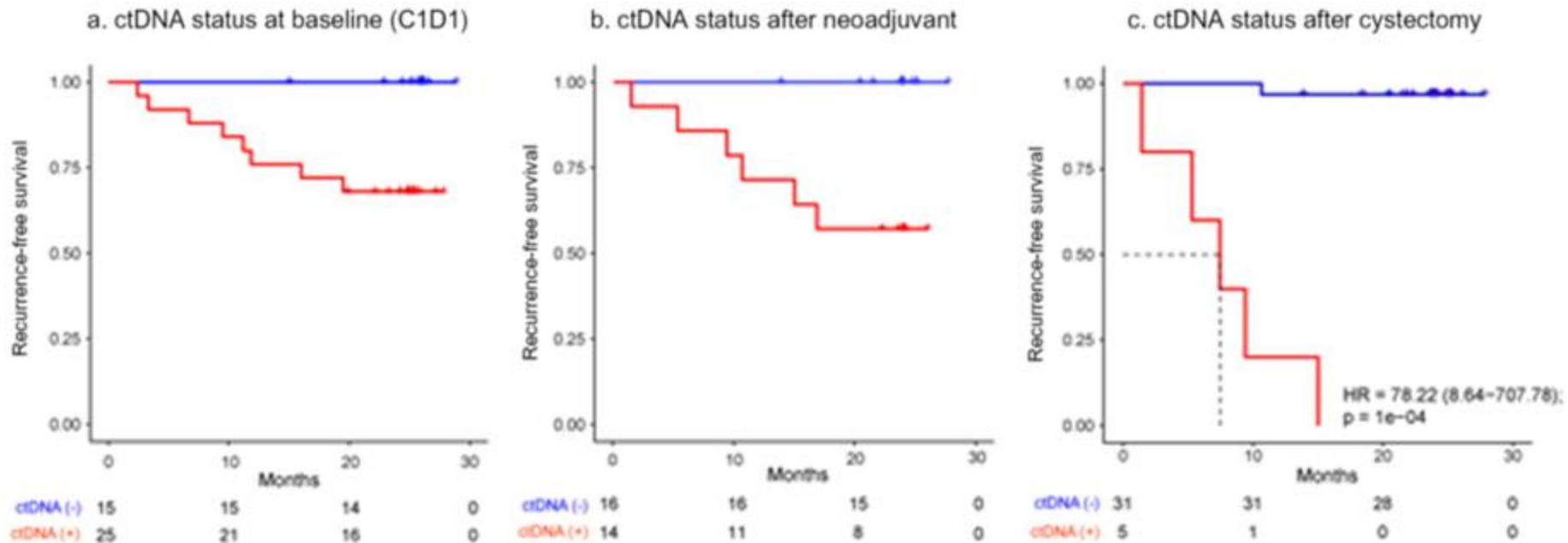
Role of ctDNA in muscle invasive bladder cancer

- Monitoring for MRD after surgery (detect recurrence before imaging)
 - In a retrospective study of 68 pts with MIBC, all 47 pts that had NEGATIVE ctDNA following RC, had RFS of 100% at 2 years
 - Better prognosis if ctDNA negative before RC



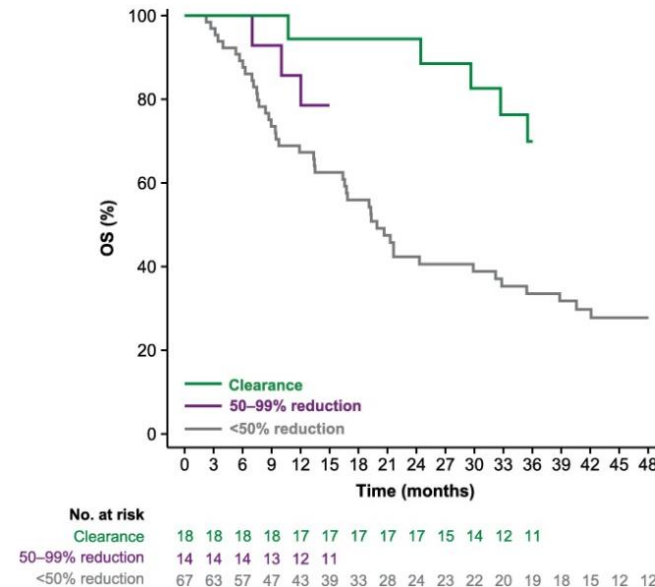
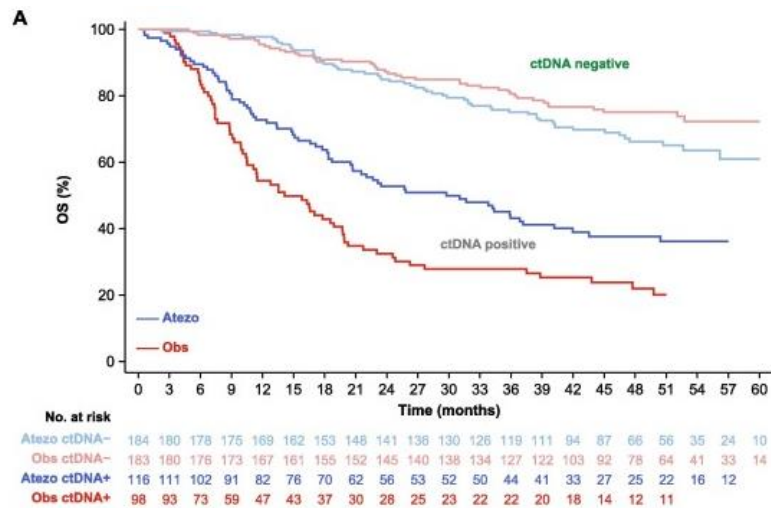
Role of ctDNA in muscle invasive bladder cancer

- Predicting response to neoadjuvant immunotherapy
 - ABACUS 2: Phase 2 trial of neoadjuvant atezolizumab in MIBC
 - ctDNA positivity associated with shorter RFS



Role of ctDNA in muscle invasive bladder cancer

- Predicting response to adjuvant immunotherapy
 - IMVIGOR 010: Phase 3 adjuvant atezolizumab in MIBC. Negative trial, did not meet primary endpoint in ITT population
 - However, interim analysis based on ctDNA status showed that:
 - ctDNA (+) associated with worse outcomes
 - ctDNA (+) identified pts with an OS benefit with atezolizumab
 - Greater reduction in ctDNA levels with atezolizumab associated with longer OS

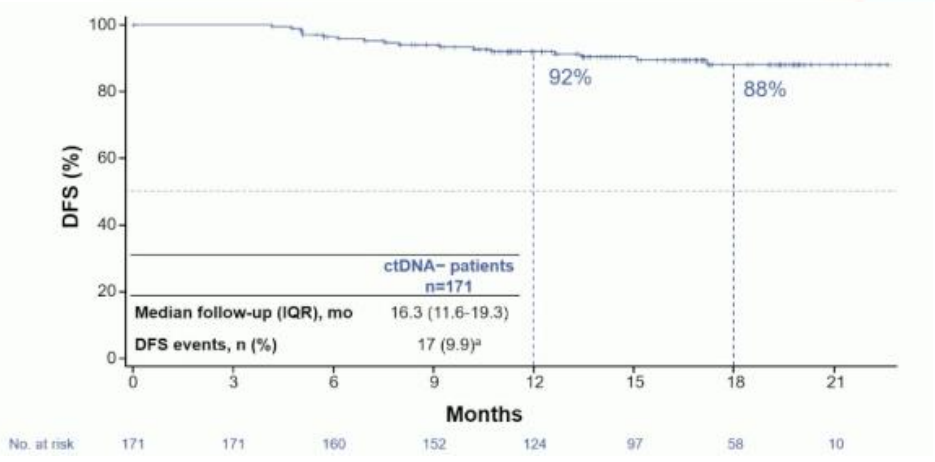
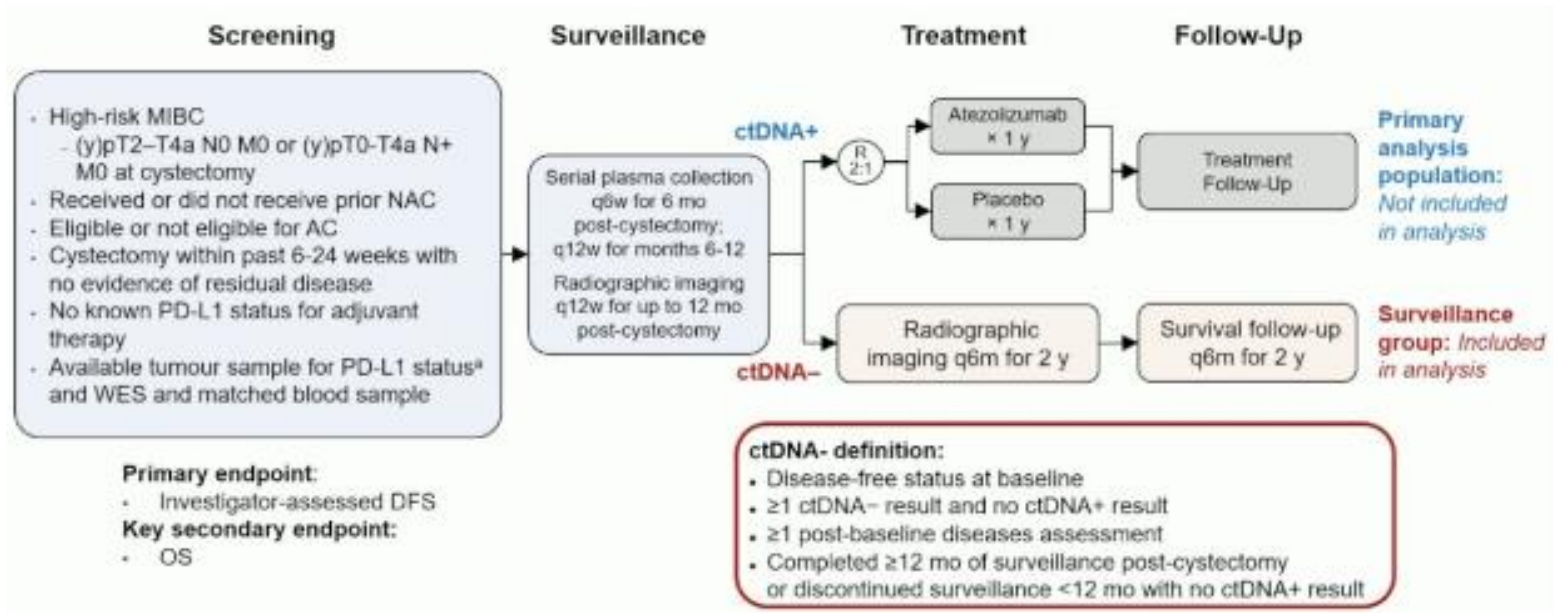


Role of ctDNA in muscle invasive bladder cancer

- Identify patients that will benefit from adjuvant treatment
 - **IMvigor011**: Adjuvant Atezolizumab in pts with high-risk MIBC who are ctDNA+
 - **TOMBOLA**: Treatment of metastatic bladder cancer at time of biochemical relapse following radical cystectomy
 - **MODERN**: An integrated Phase 2/3 trial of mrd-optimization of adjuvant therapy in urothelial cancer

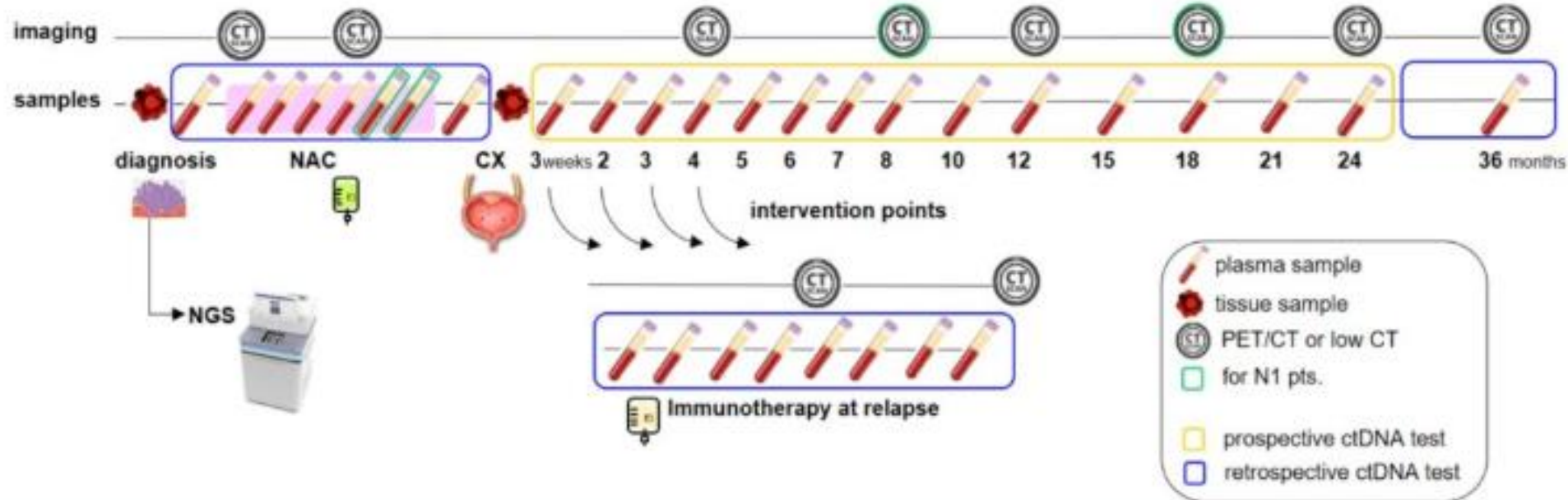
Role of ctDNA in muscle invasive bladder cancer

- IMvigor011:



Role of ctDNA in muscle invasive bladder cancer

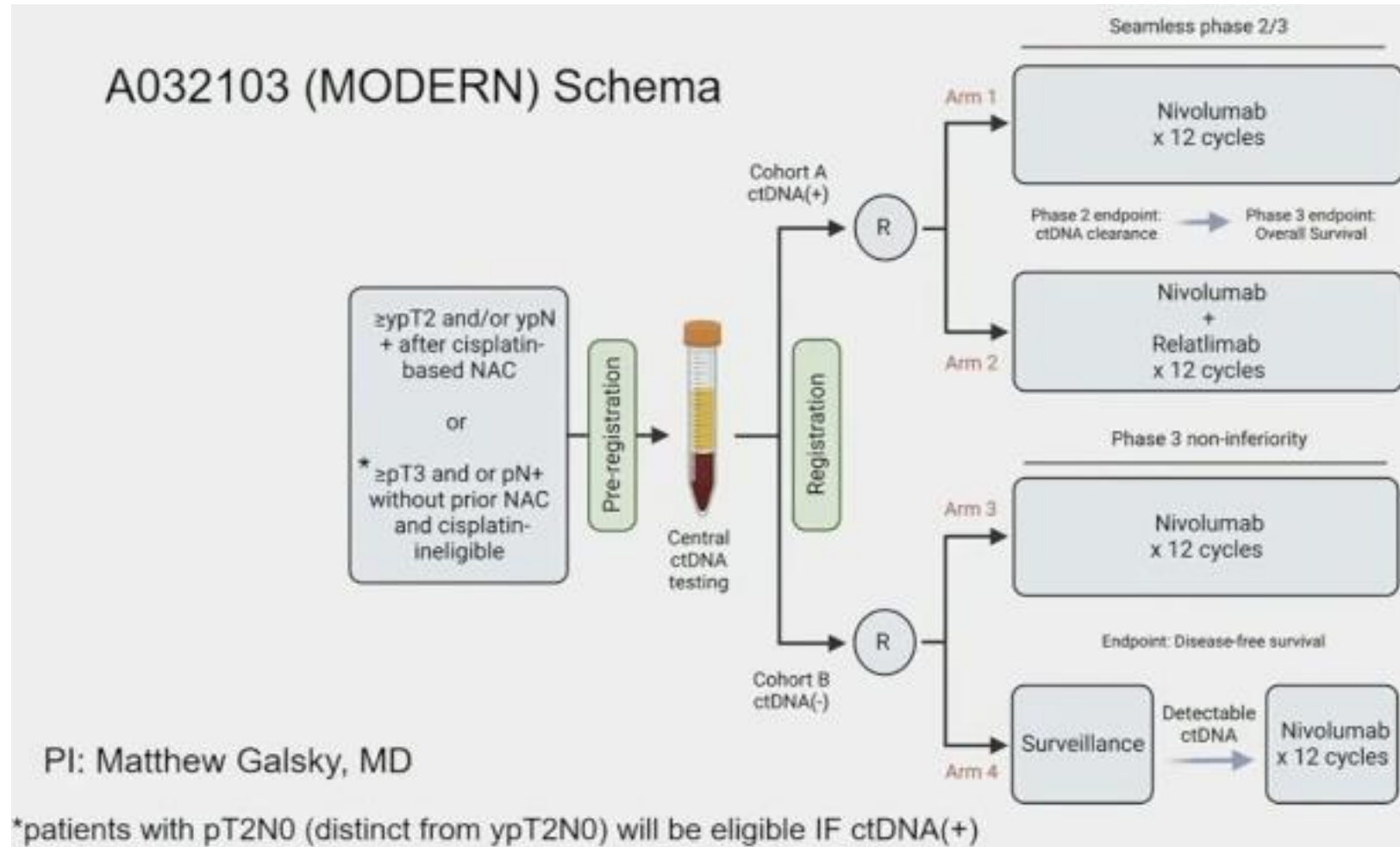
- TOMBOLA: Non-randomized ctDNA based intervention study



- Plan to enroll 282 patients. Study accrual will continue until 127 patients who are ctDNA positive begin treatment

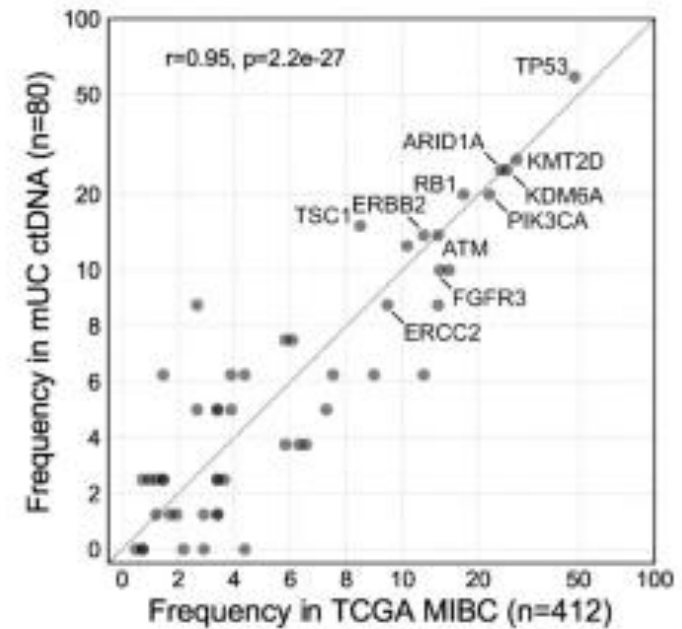
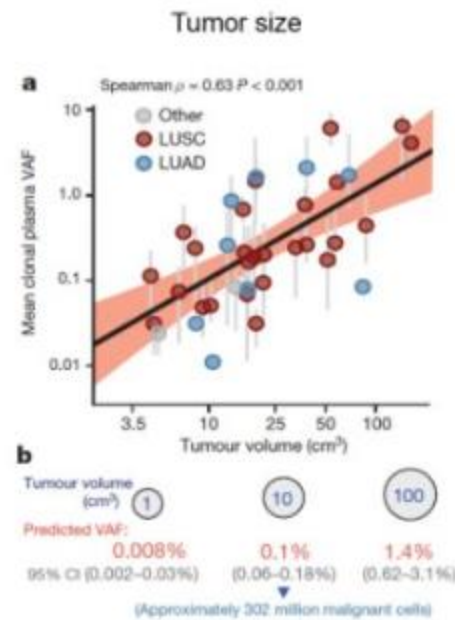
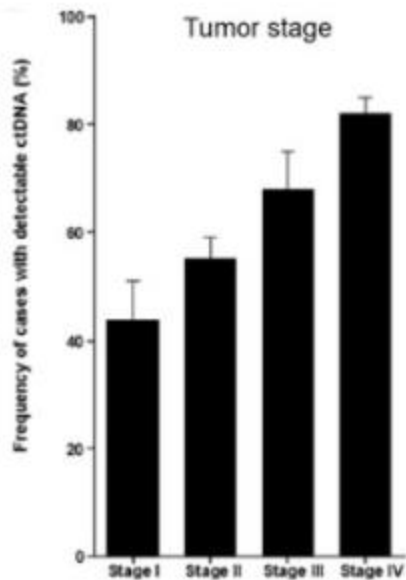
Role of ctDNA in muscle invasive bladder cancer

- MODERN:



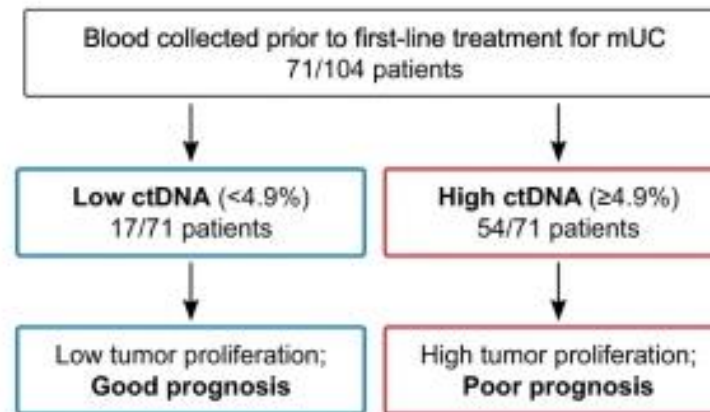
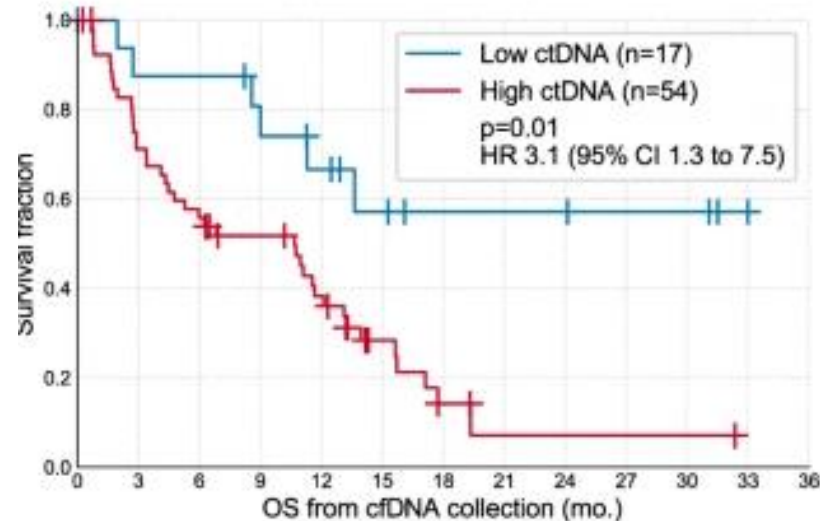
Correlation of ctDNA and tumor burden

- ctDNA burden increases with stage
- High concordance of genetic alterations (FGFR3 and ERBB2) between tissue and ctDNA



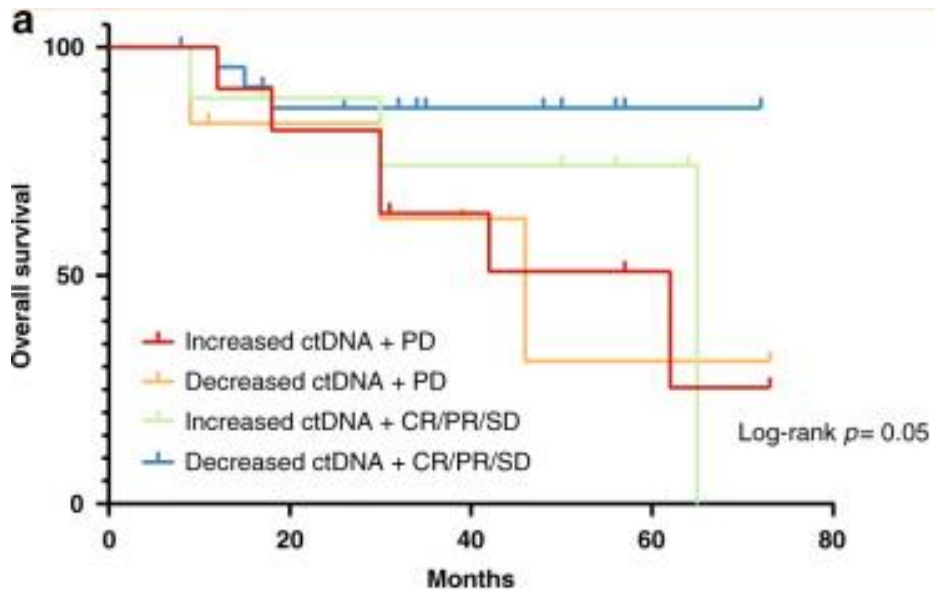
Role of ctDNA in metastatic bladder cancer

- Potentially prognostic role of ctDNA in mUC setting
 - Lower ctDNA burden independently prognostic for overall survival in patients initiating 1L systemic treatment
 - Needs to be validated in prospective studies



Role of ctDNA in metastatic bladder cancer

- Potentially predictive role of ctDNA in mUC setting
 - Serial ctDNA analysis may predict disease progression
 - Needs to be validated in prospective studies

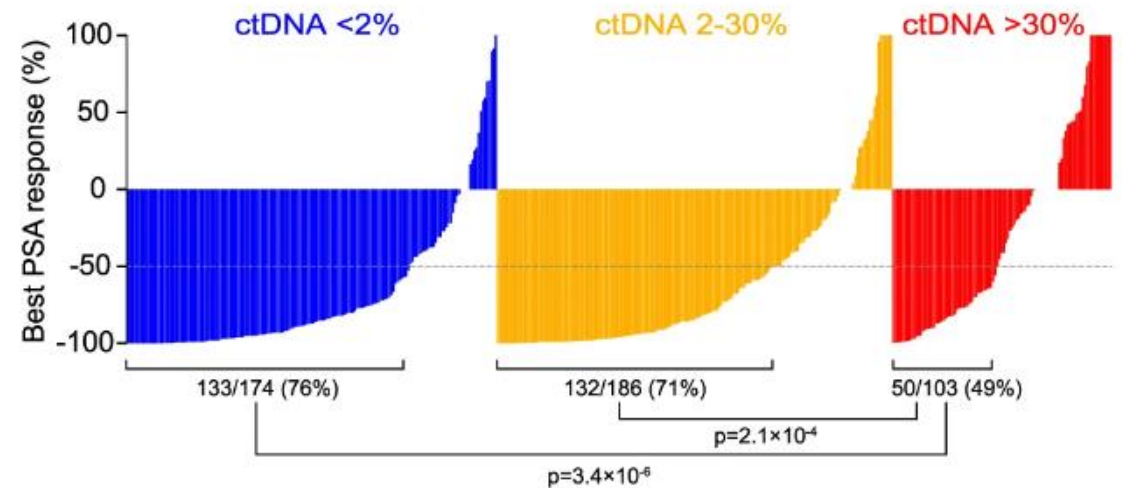
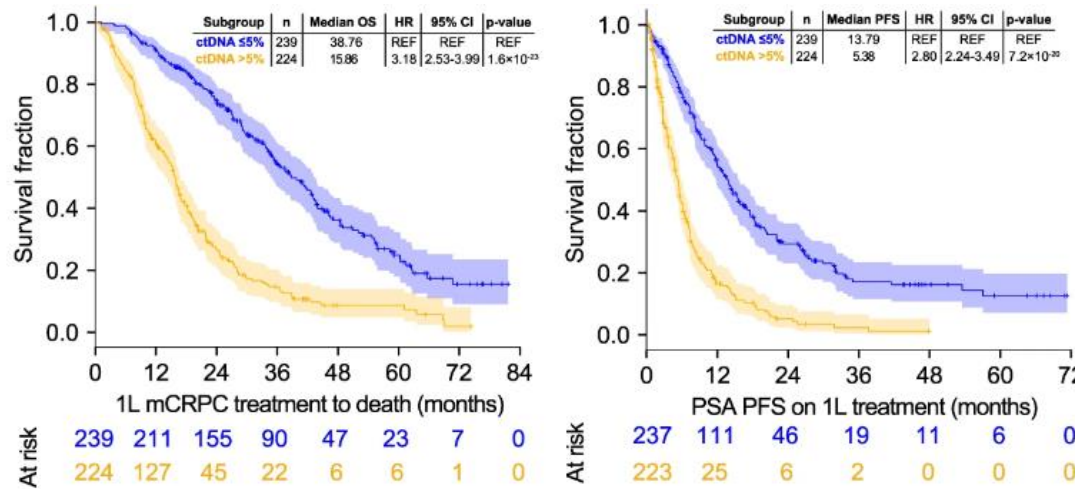


Role of ctDNA in prostate cancer

- Potential predictive marker for overall survival, progression-free survival, and treatment response in mCRPC
- Prognostic role for response/outcomes with ARSI in mCRPC
- Identify emerging resistance to therapy and expansion of new mutations/alterations

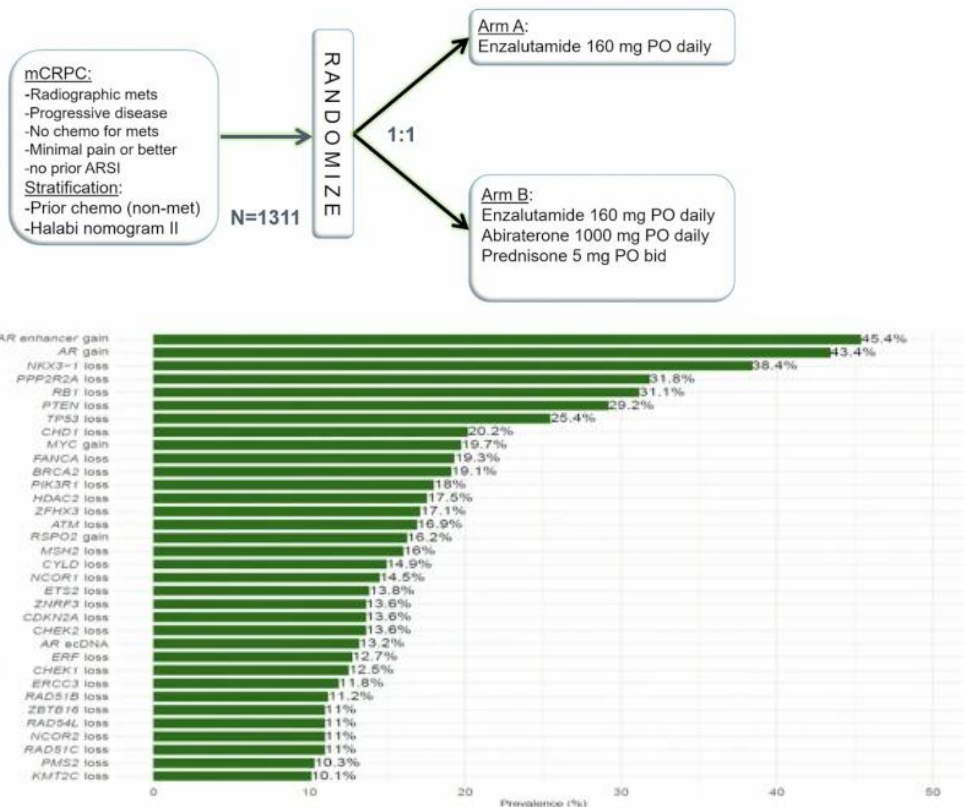
Role of ctDNA in prostate cancer

- Baseline ctDNA% strongly predicts overall survival, progression-free survival, and treatment response in mCRPC

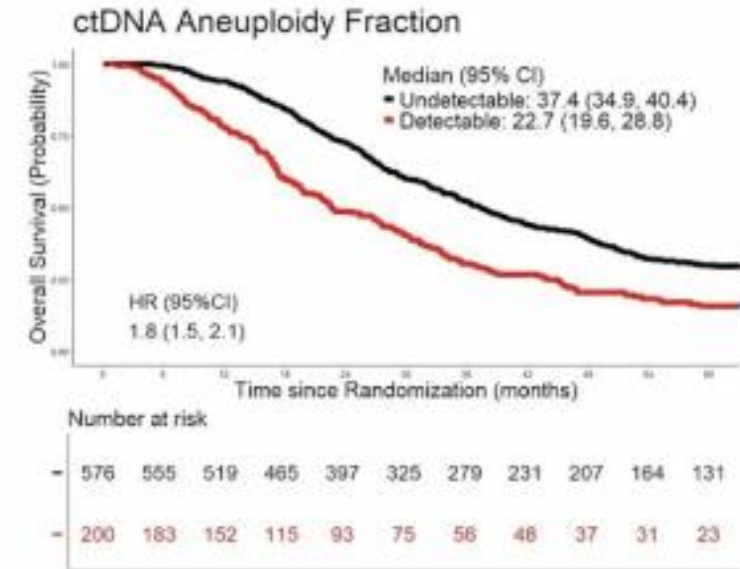


Role of ctDNA in prostate cancer

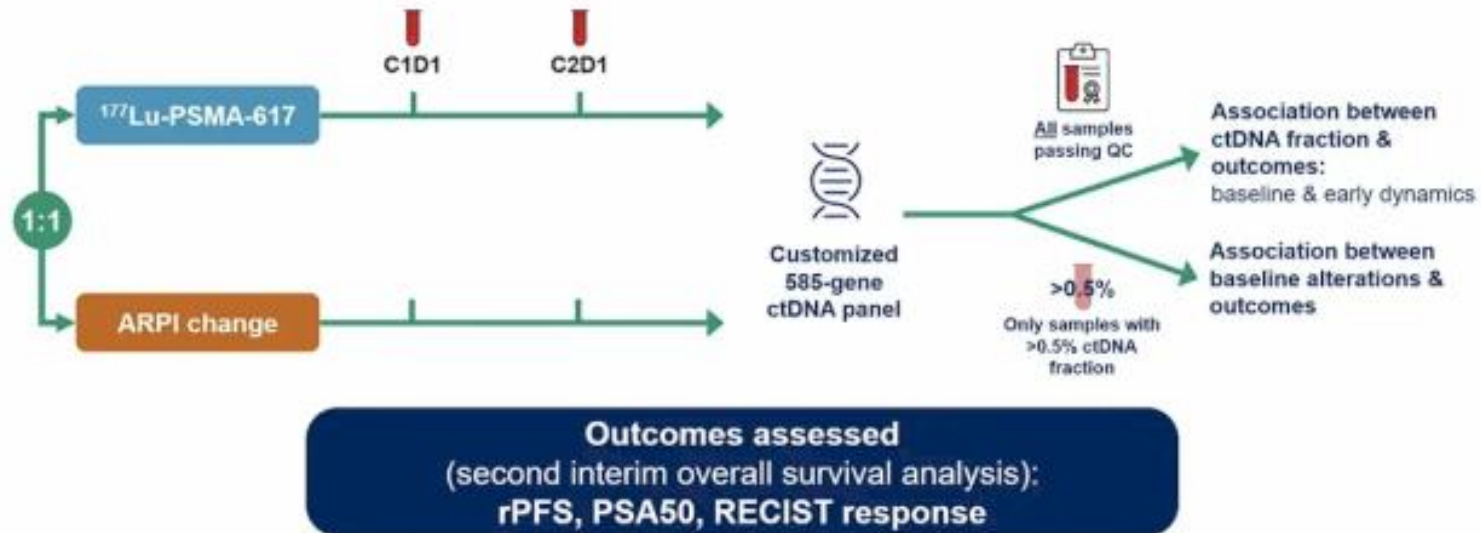
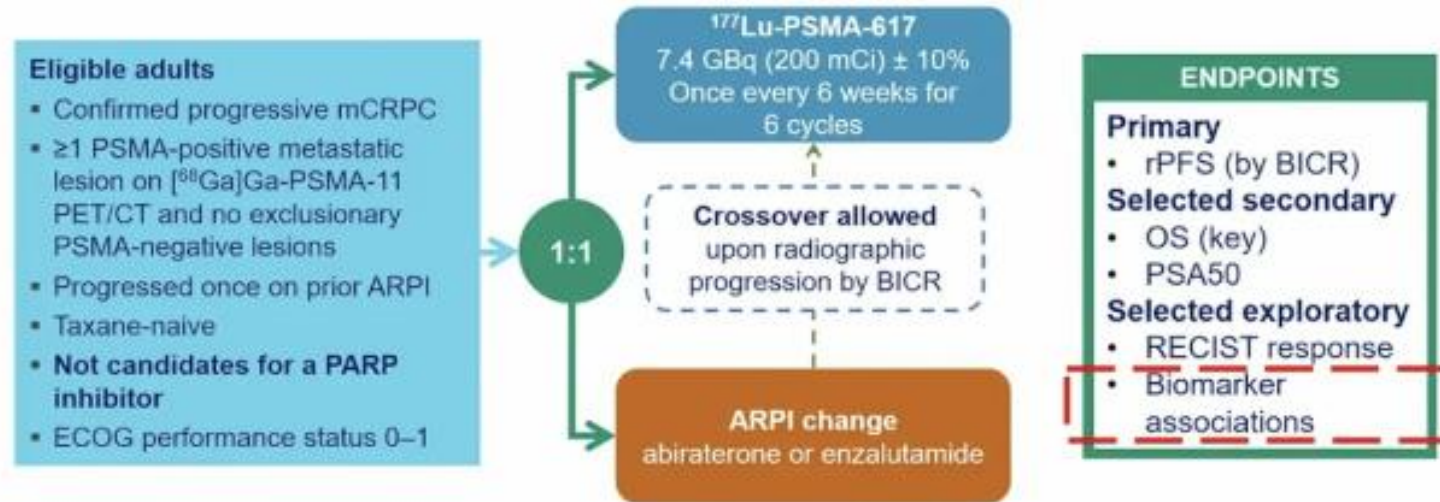
- Prognostic role for response/outcomes with ARSI in mCRPC
 - A Clinical-Genetic ctDNA-Based Prognostic Model for Predicting OS in Men with mCRPC Treated with Potent Androgen Receptor Inhibition (Alliance)



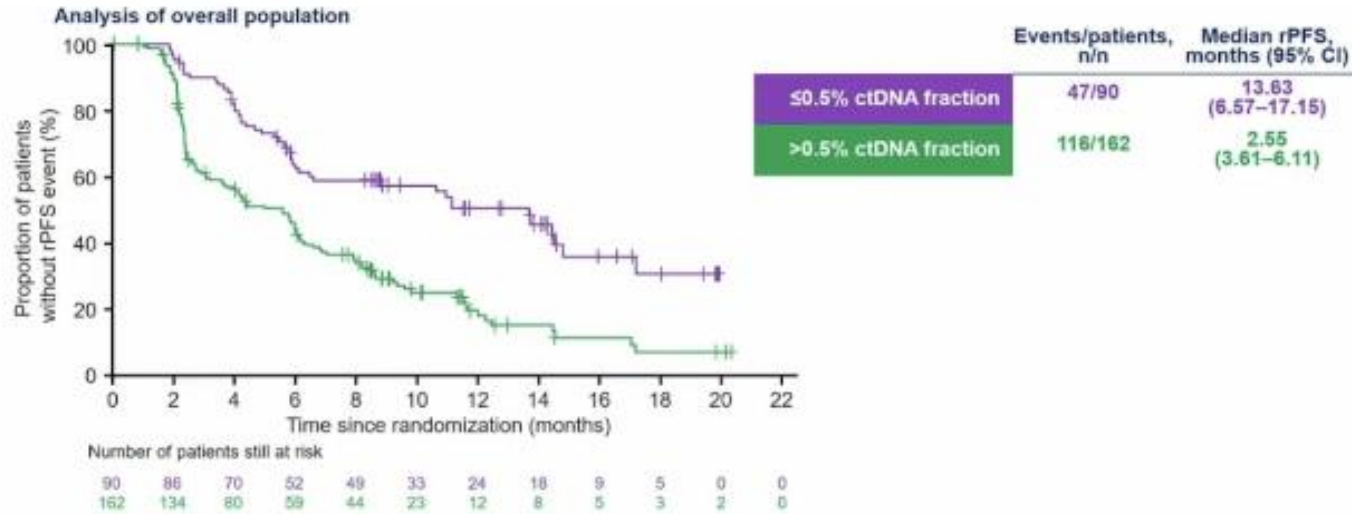
KM Overall Survival by ctDNA Aneuploidy Fraction



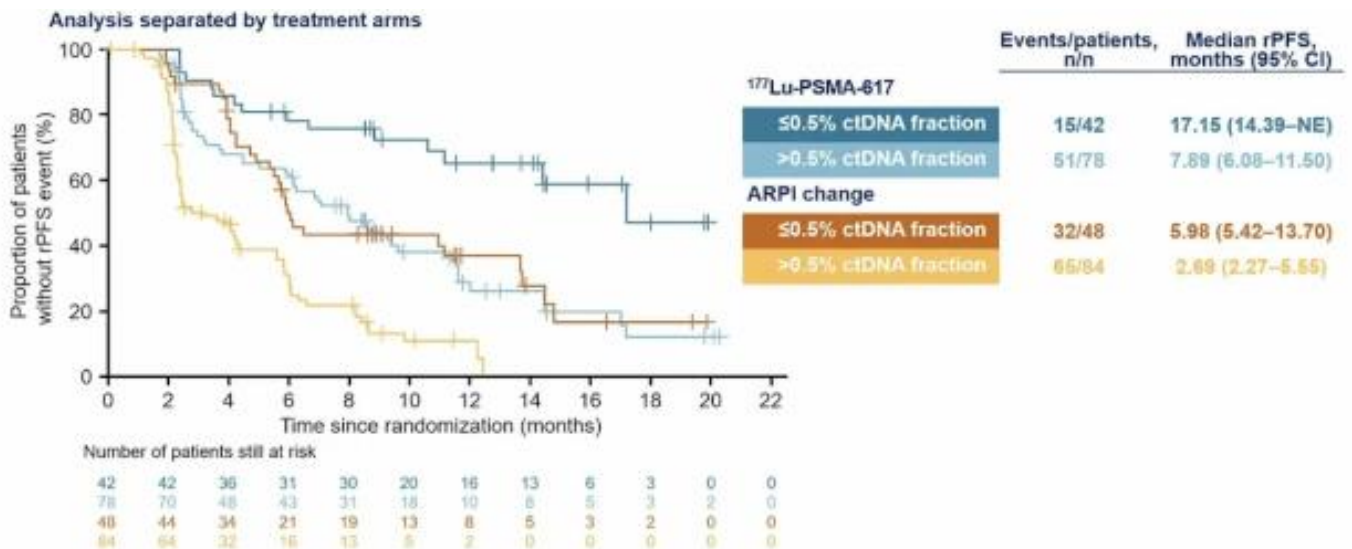
Role of ctDNA in prostate cancer- PSMAfore



Role of ctDNA in prostate cancer- PSMAfore

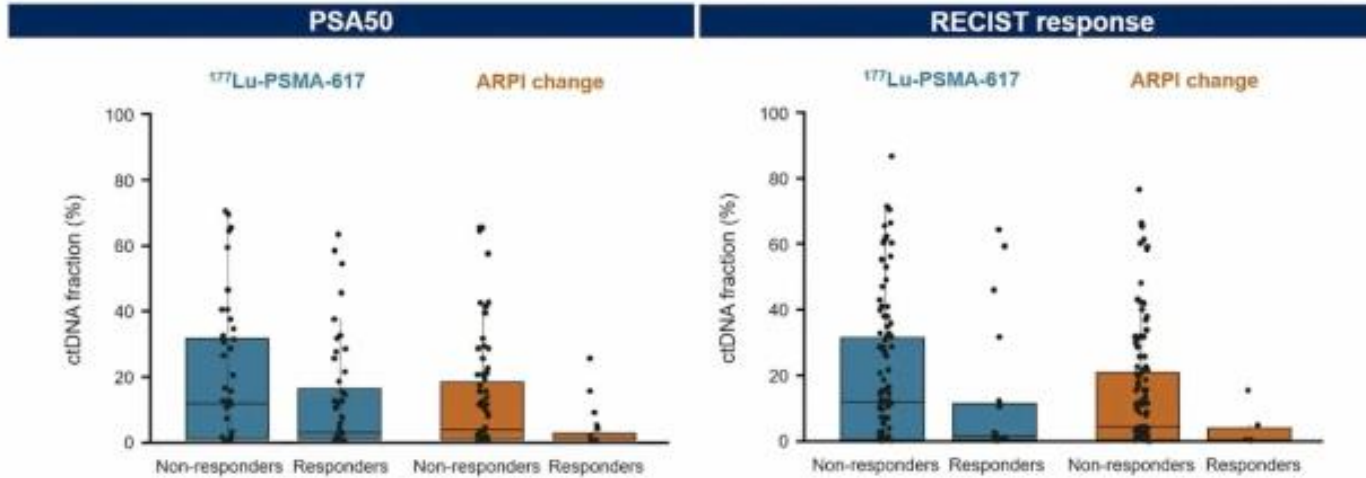


- Higher baseline ctDNA fraction associated with worse/shorter rPFS in both treatment arms

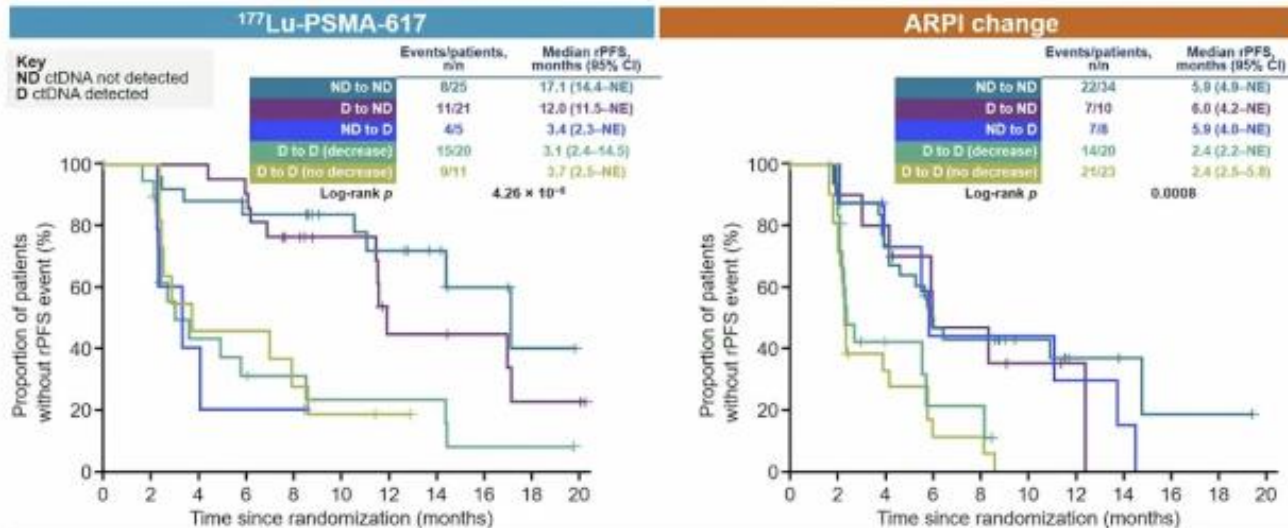


- Improved rPFS with Pluvicto if low ctDNA fraction ($\leq 0.5\%$)

Role of ctDNA in prostate cancer- PSMAfore



- Higher baseline ctDNA fraction (>0.5%) associated with worse RECIST response and PSA50 in both Lu-PSMA-617 and ARSI arms

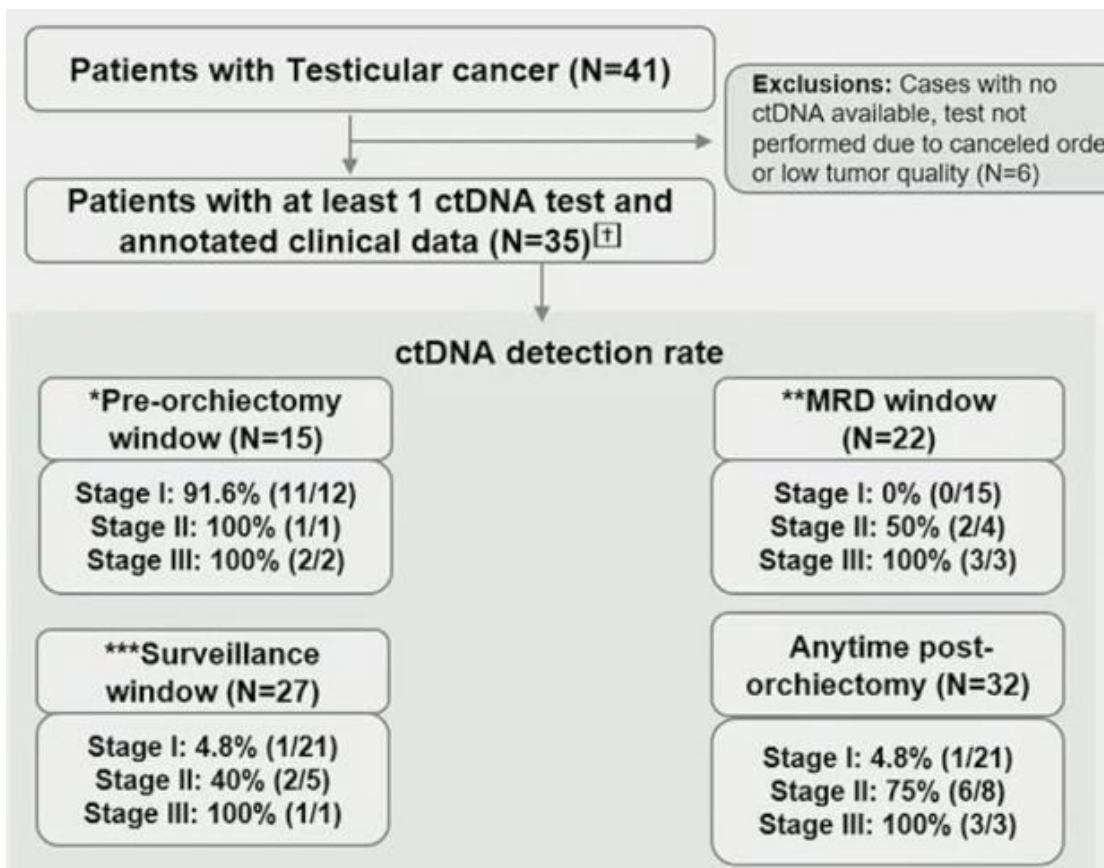


- Early ctDNA clearance associated with improved rPFS in both Lu-PSMA-617 and ARSI arms

ctDNA in Testicular Germ Cell Tumors

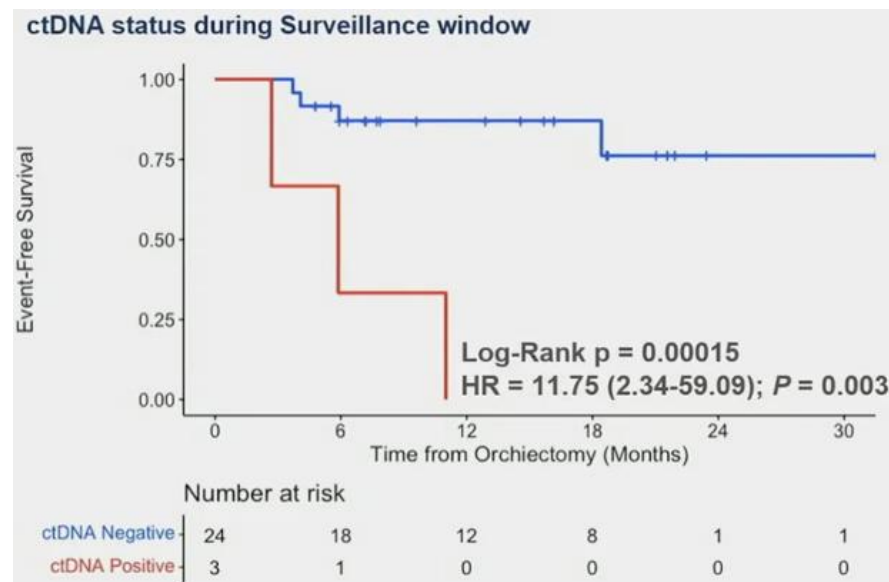
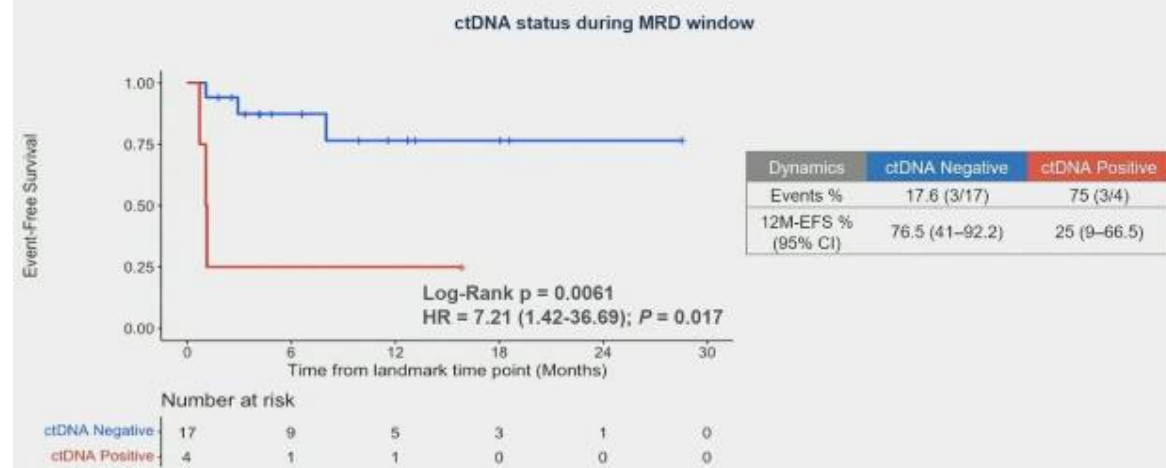
- Two recent studies at GU ASCO 2024
- Utilized Signatera tumor-informed assay
- ctDNA may predict recurrence
- Needs to be validated in large prospective studies, both cohorts were small
- Role with miR371?

ctDNA in Testicular Germ Cell Tumors

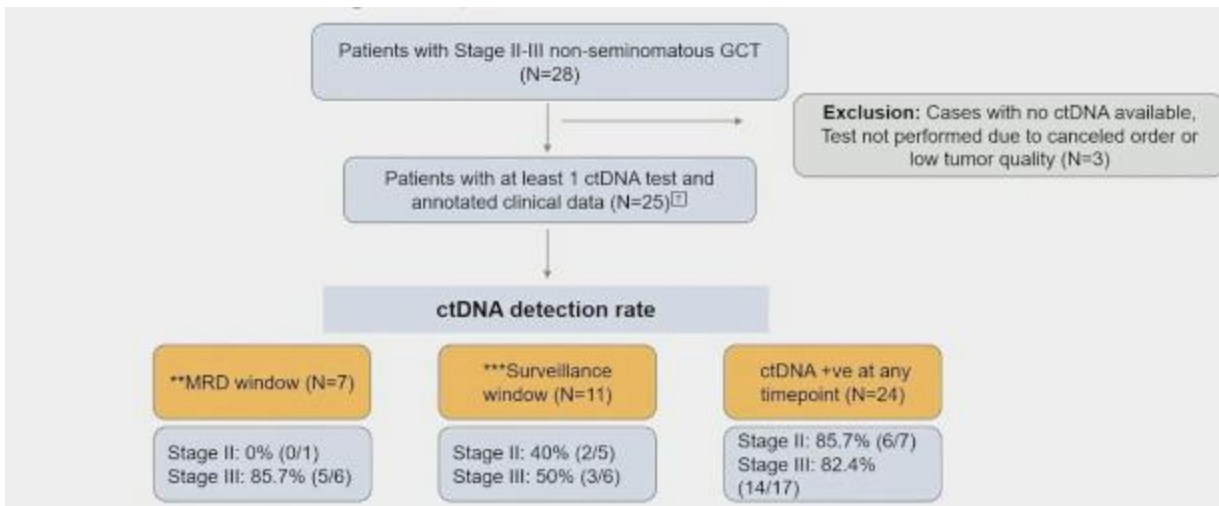


Results: ctDNA-positivity at the MRD window is associated with inferior EFS

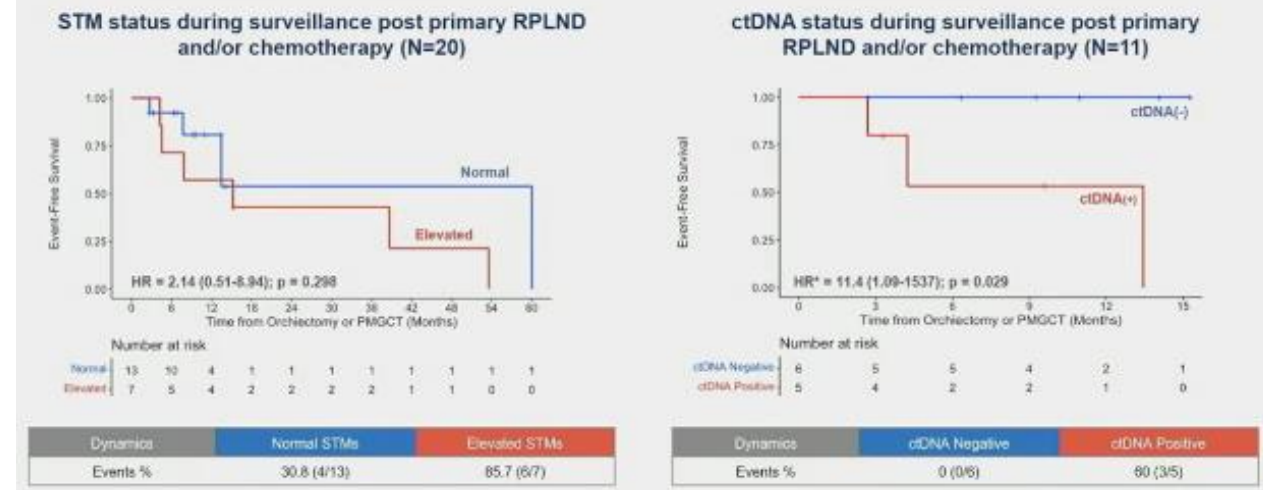
MRD window: 1-12 weeks post-orchidectomy, prior to start of any first line therapy - Landmark 12 weeks



ctDNA in Testicular Germ Cell Tumors



Association of STM and ctDNA with EFS post RPLND for stage II and post chemotherapy for advanced disease



Thank You

