Clinical utility of ctDNA analysis in bladder cancer

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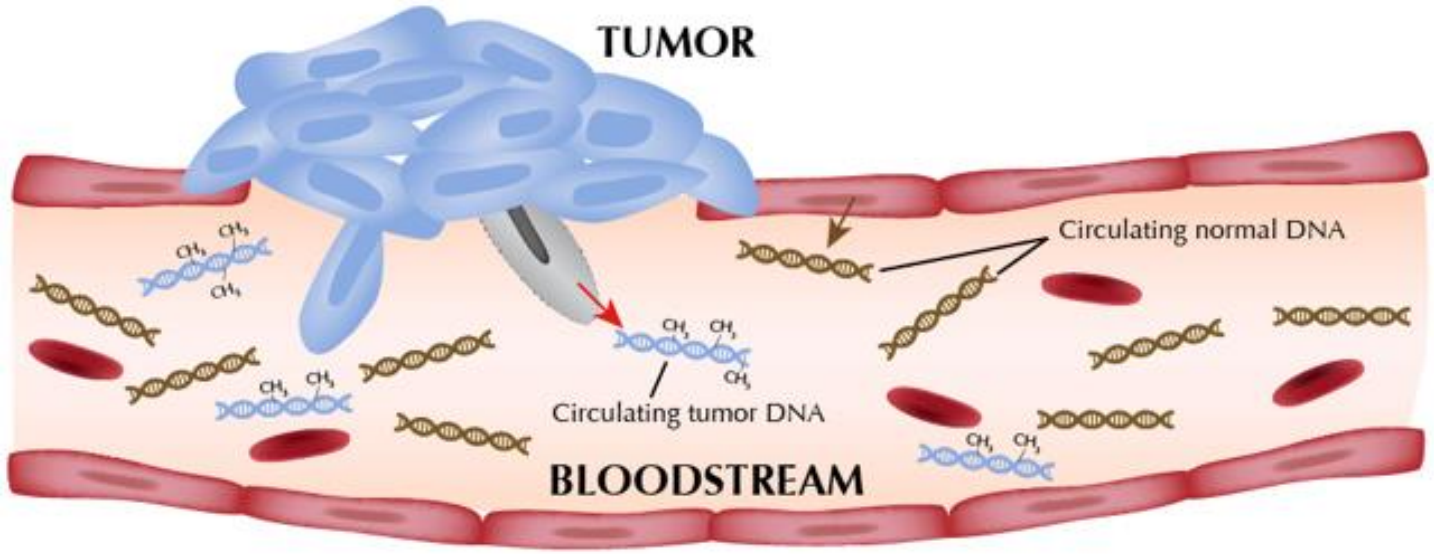
Disclosures

- **Travel, research funding:**
  Roche, Genentech, MSD, Pfizer, BMS

- **Honoraria:**
  Merck, Roche, Pfizer, Ellipses, Ipsen

- **Participating investigator** on studies with Roche/GNE, Pfizer, MSD, Exelixis, BMS, Astellas, AstraZeneca

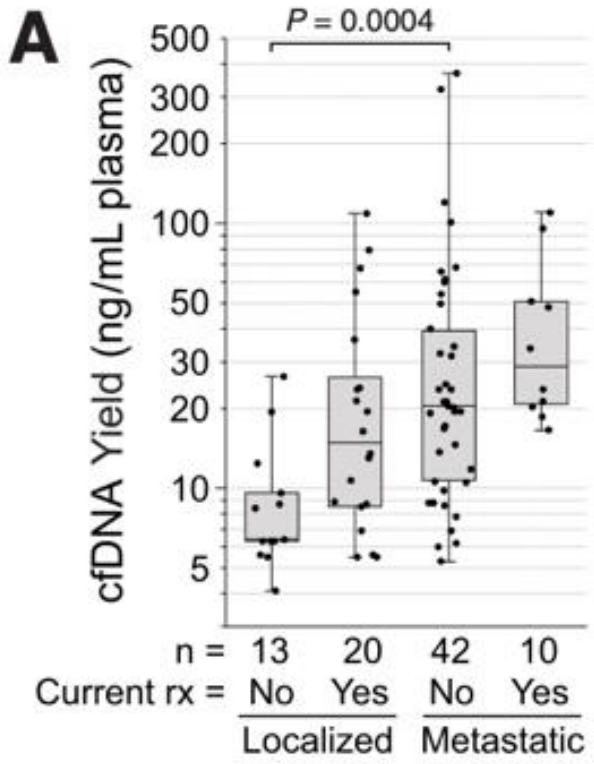
Circulating tumour DNA (ctDNA)

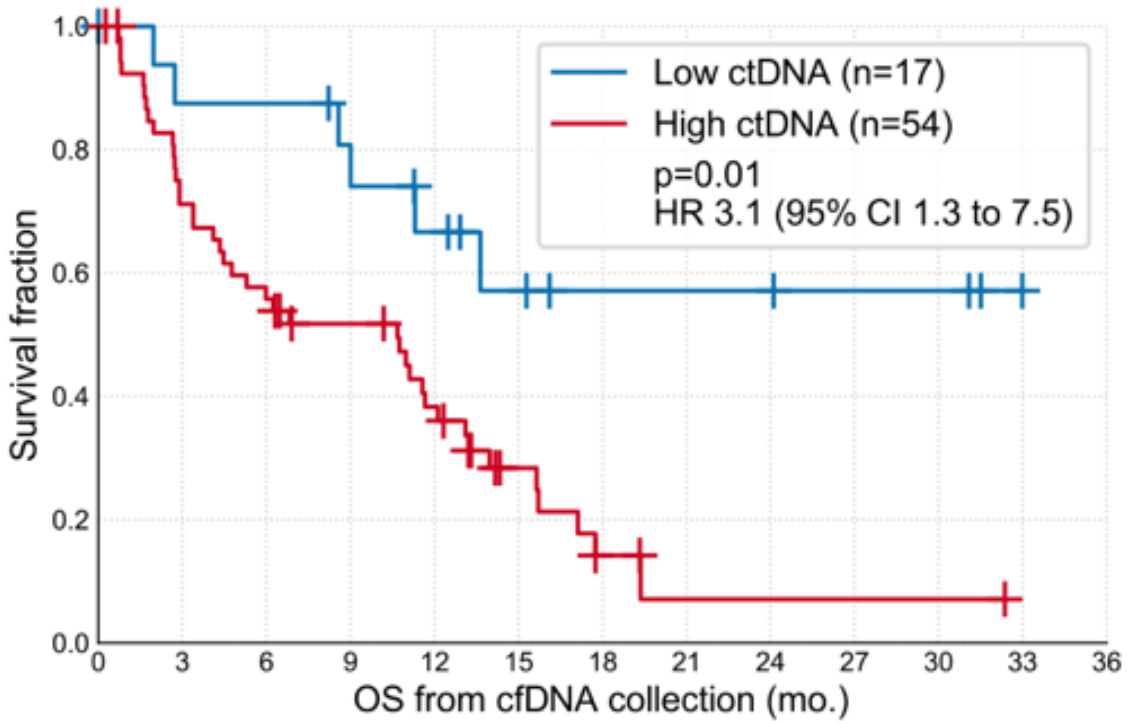


Cell-free DNA
spontaneous release of DNA from healthy cells, blood cells, bacteria

Circulating tumour DNA
released through necrotic cells, apoptosis, active secretion
cleared through elimination via liver or kidney
short half-life: mins - hours

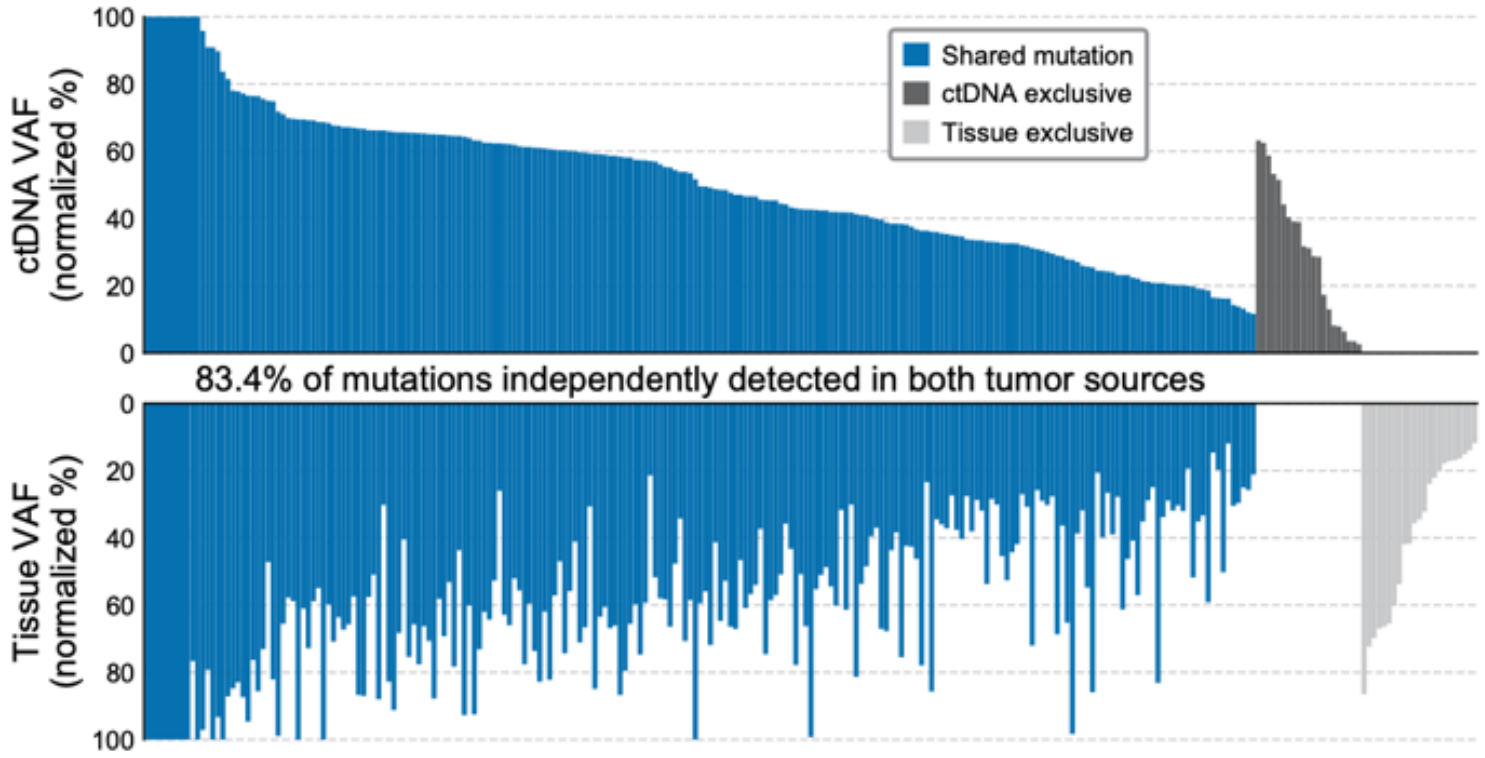
ctDNA correlates with disease burden and prognosis





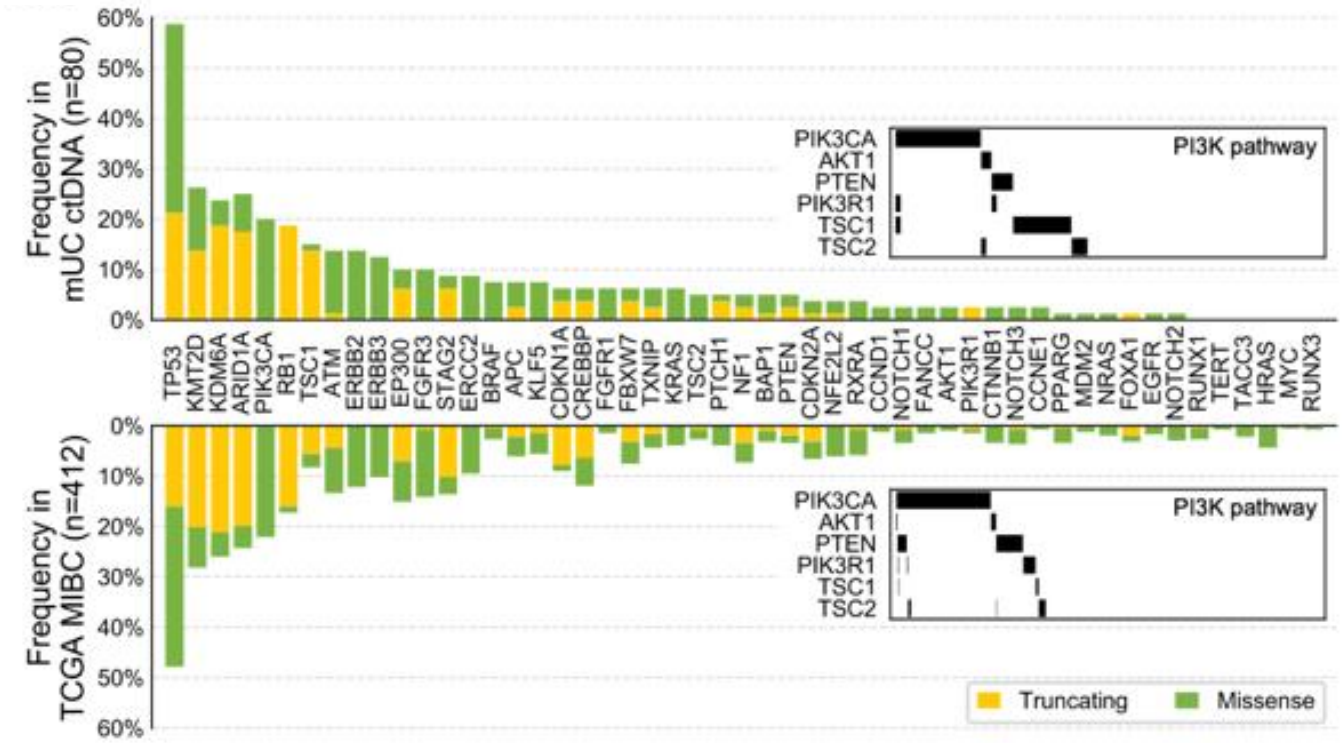
Vandekerkhove et al., Clin Can Res 2017; Vandekerkhove et al., Nat Comm 2021

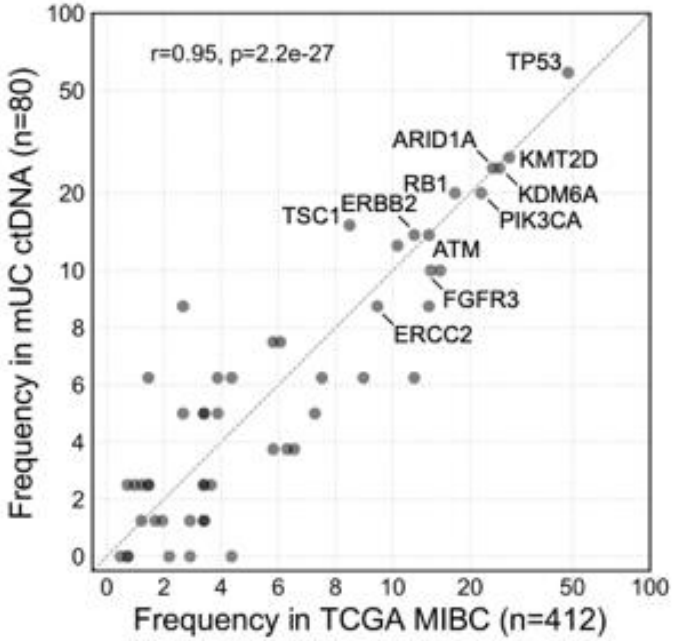
High concordance between ctDNA and matched tissue



Vandekerkhove et al., Nat Comm 2021

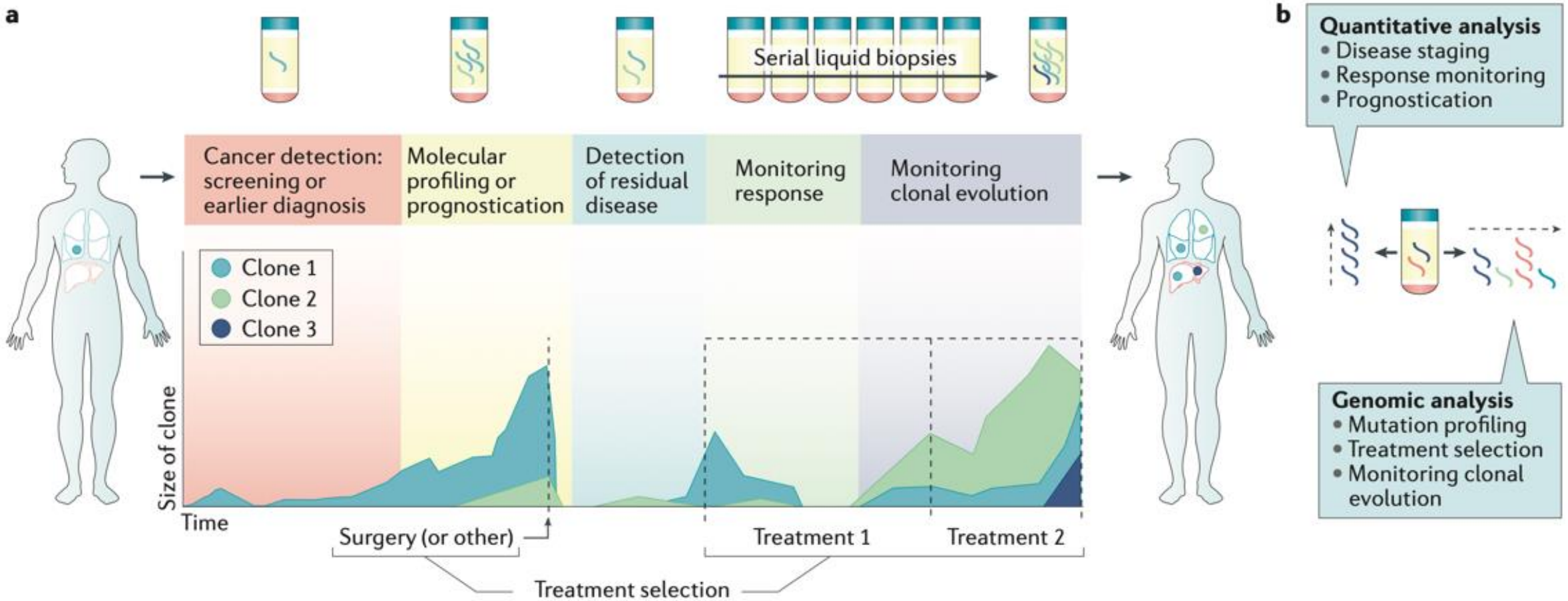
Mutation type and frequency of mUC ctDNA similar to TCGA MIBC cohort





Vandekerkhove et al., Nat Comm 2021

Current ctDNA applications



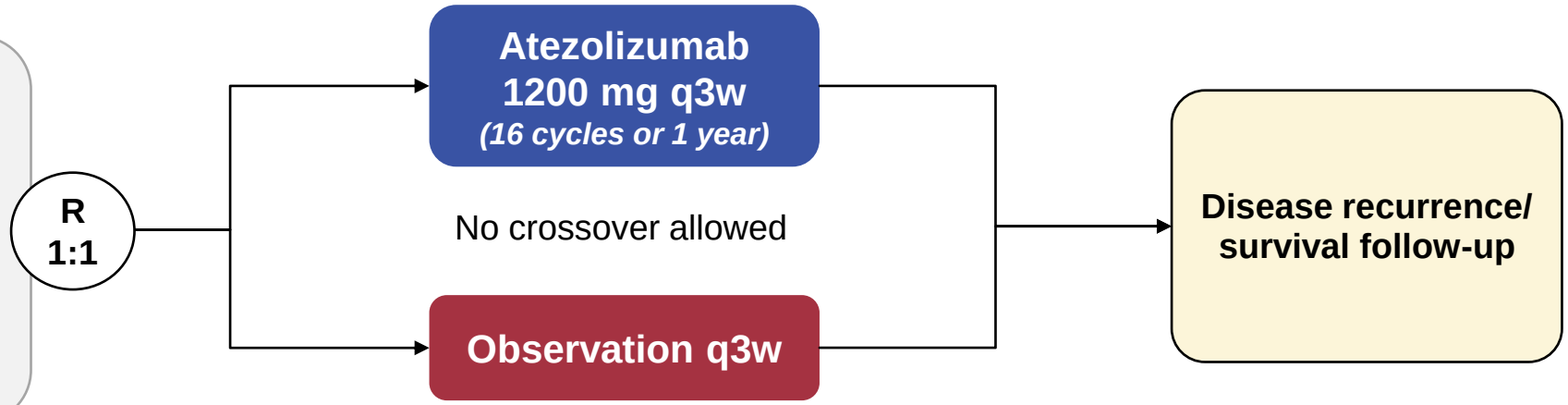
Wan et al., Nat Rev Cancer 2017

Detection of minimal residual disease (MRD)

Phase 3 IMvigor010 adjuvant study in MIBC

Key eligibility

- High-risk MIUC (bladder or upper tract)
- Radical surgery with lymph node dissection within ≤14 weeks
- Tissue sample for PD-L1 testing



Endpoints

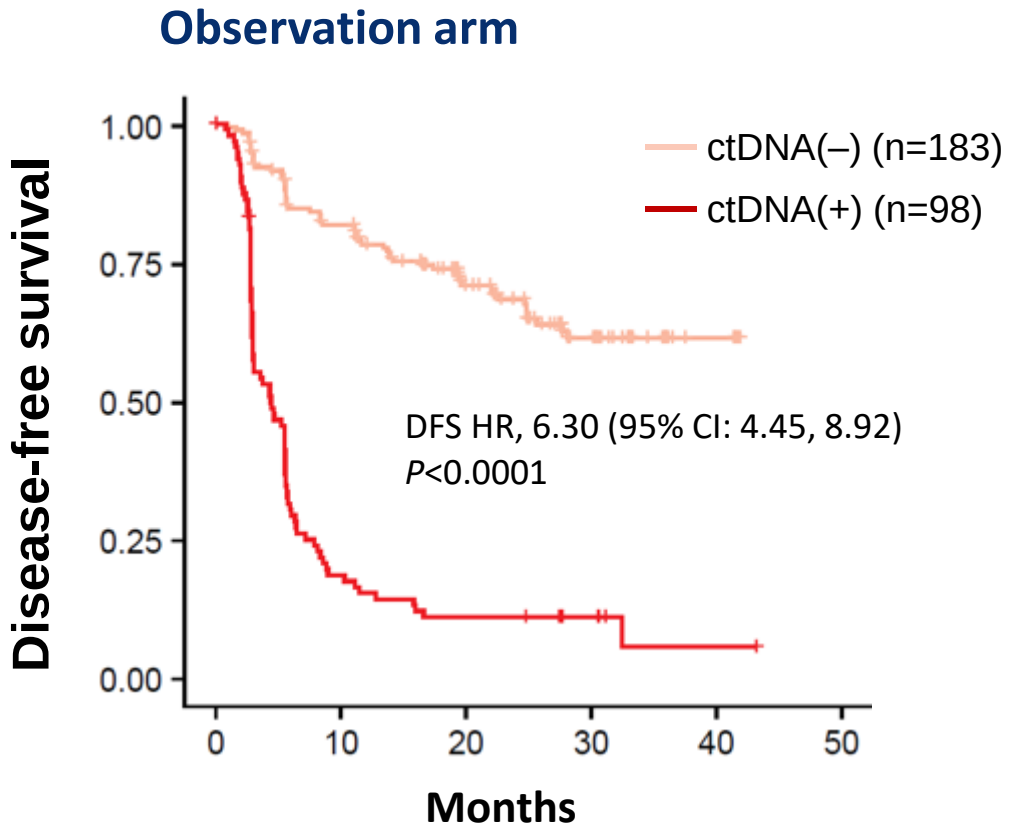
- Primary: DFS (ITT population)
- Key secondary: OS (ITT population)
- Other: Safety
- **Exploratory: predictive, prognostic and pharmacodynamic biomarkers in tumour tissue and blood and their association with disease recurrence**

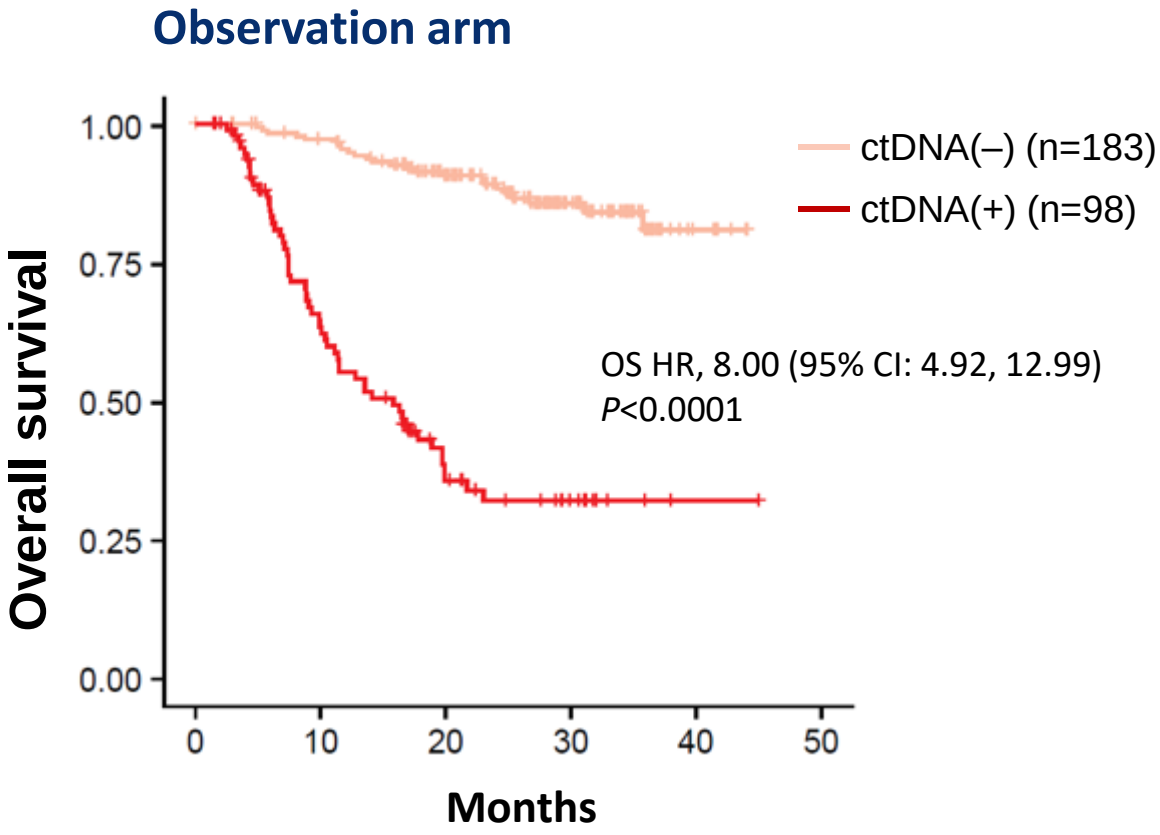
- IMvigor010 did not meet its primary endpoint (DFS in the ITT population)[1]
  - A pre-planned interim OS analysis was performed but could not be formally tested
  - OS follow-up is immature and ongoing in the ITT population
- The PD-L1 and TMB biomarkers did not identify patients benefitting from atezolizumab vs observation in the ITT population
- A pre-specified ctDNA biomarker analysis was performed

ClinicalTrials.gov ID, NCT02450331.
IC, tumour-infiltrating immune cells; q3w, every 3 weeks. TMB, tumour mutational burden. 1. Hussain M, et al.

Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

ctDNA(+) patients have poor prognosis



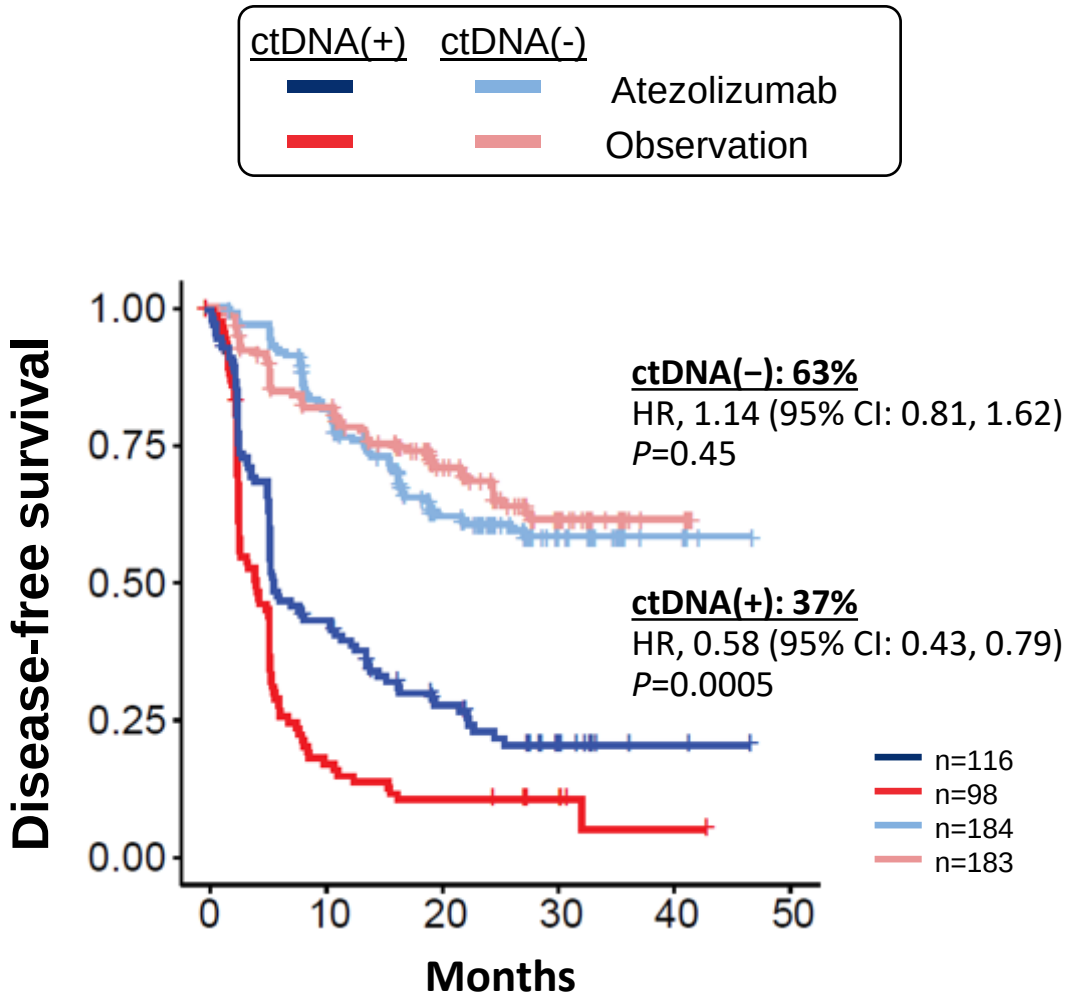


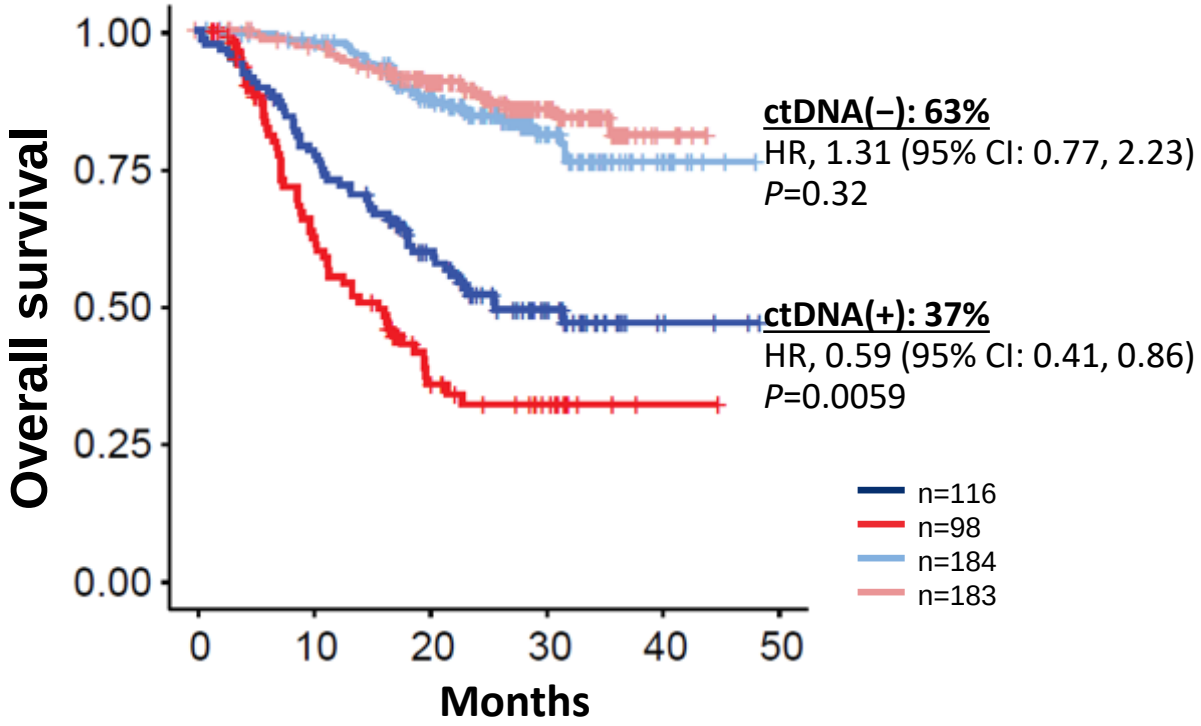
- IMvigor010 confirmed the prognostic value of ctDNA status

Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

ctDNA(+) patients in the BEP had improved DFS and OS with atezolizumab vs observation

	ctDNA(+) patients	
	Atezolizumab	Observation
Median DFS (95% CI), mo	5.9 (5.6, 11.2)	4.4 (2.9, 5.6)
Median OS (95% CI), mo	25.8 (20.5, NR)	15.8 (10.5, 19.7)

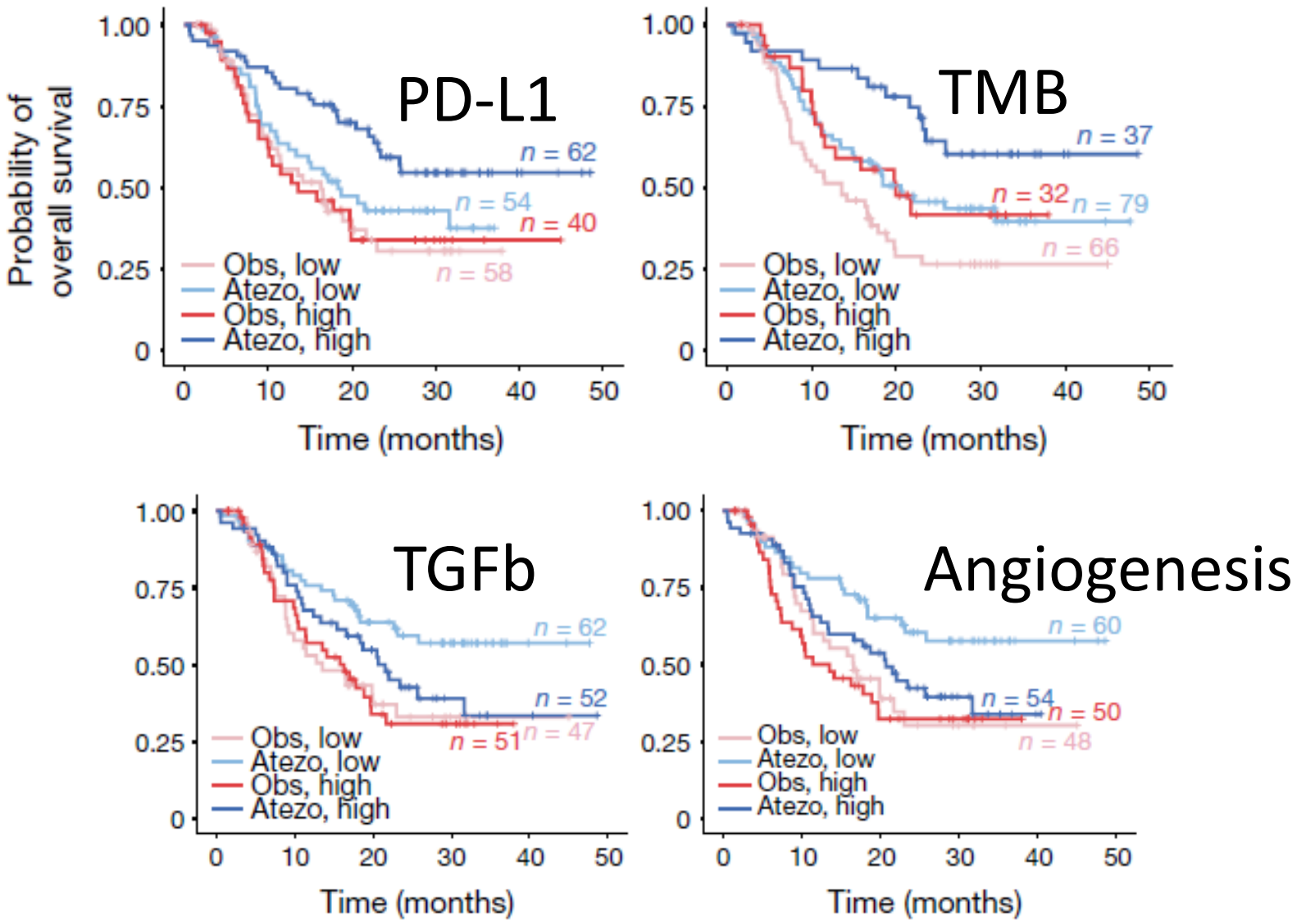




NR, not reached.

Powles et al. IMvigor010 ctDNA

Outcome in ctDNA+ve patients is related to tissue based immune biomarkers



Powles et al Nature 2021

FDA Grants Two New Breakthrough Device Designations for Natera's Signatera™ MRD Test

Designations help accelerate the regulatory review and approval of Signatera across a variety of solid tumor indications

NEWS PROVIDED BY
Natera, Inc. →
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Medicare Extends Coverage of Natera's Signatera™ MRD Test to Muscle Invasive Bladder Cancer

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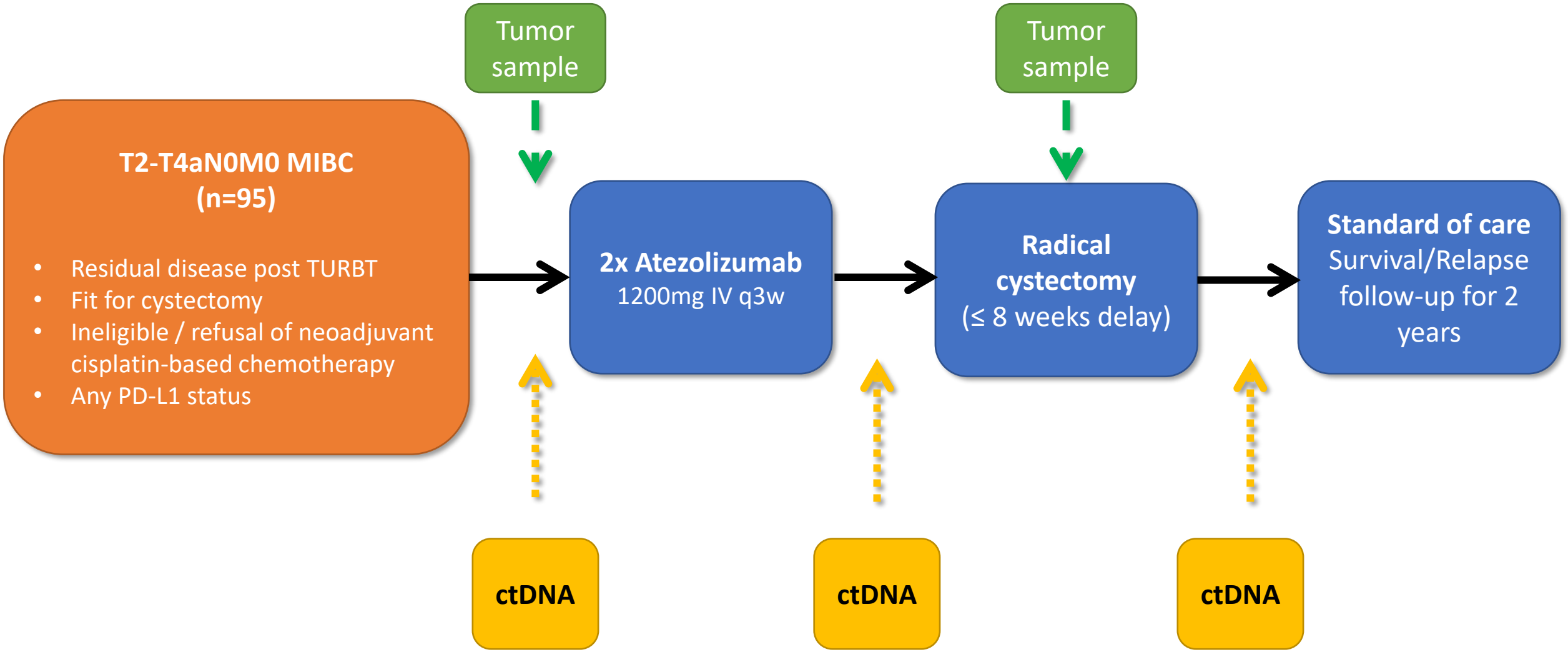
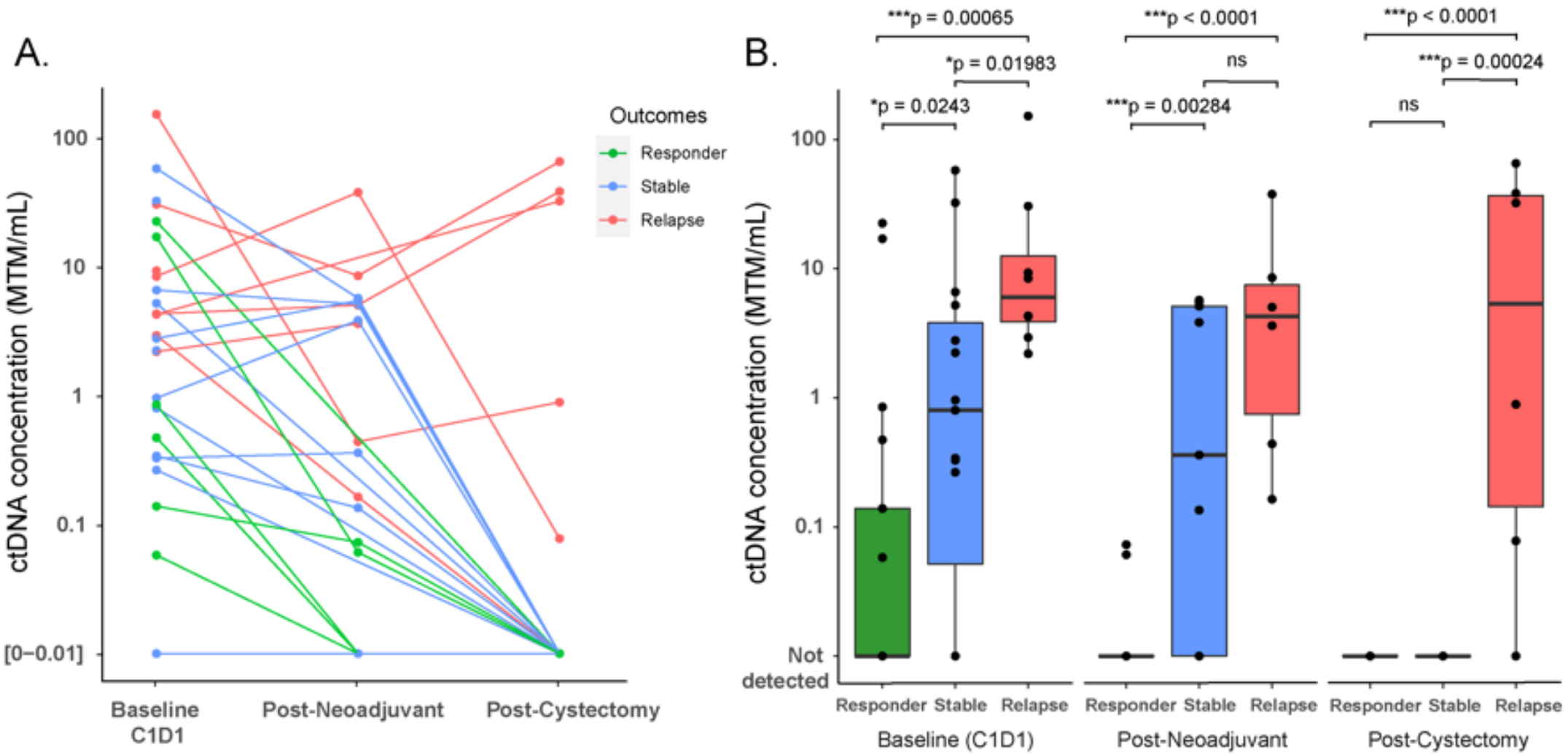
Measurement of treatment response

ABACUS



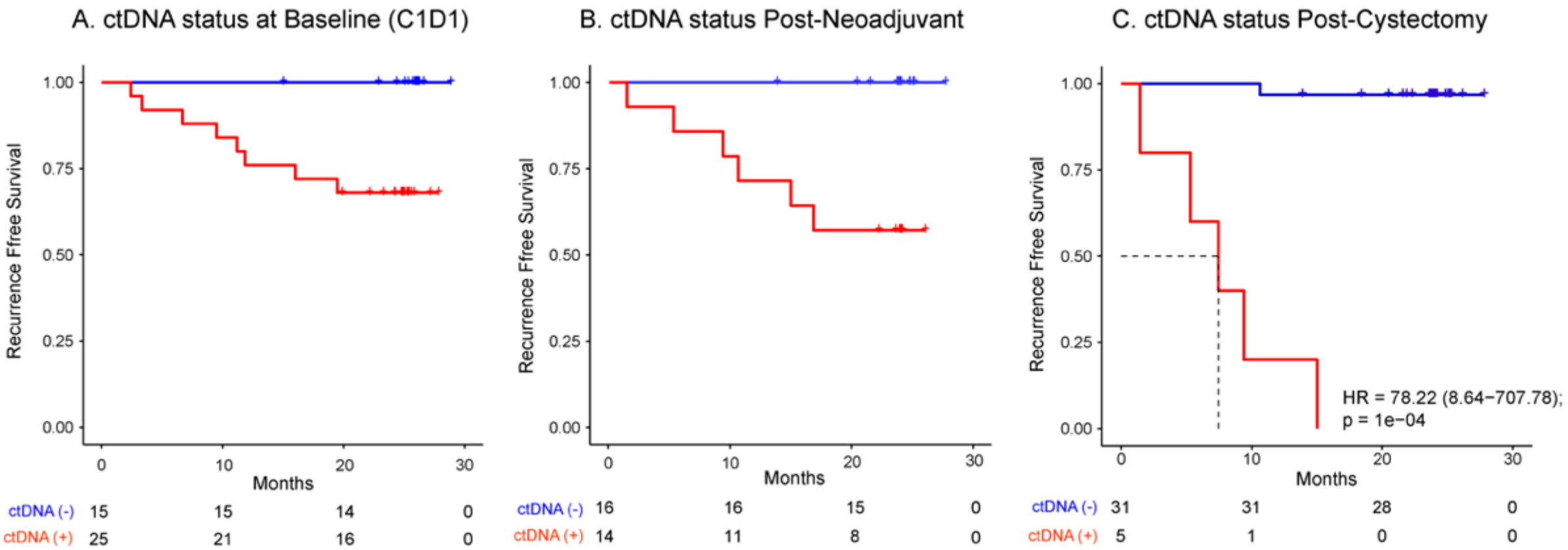
Powles et al., Nat Med 2019

Correlation between ctDNA and response



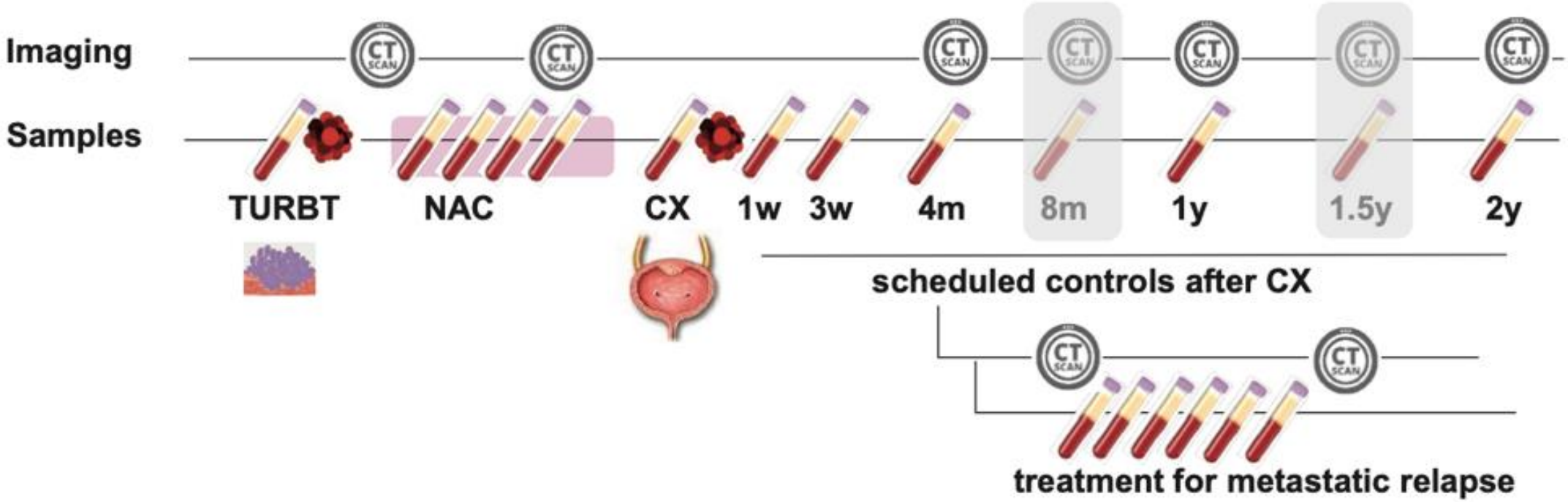
Szabados et al., Eur Urol, 2022

Correlation between ctDNA and survival



Szabados et al., Eur Urol, 2022

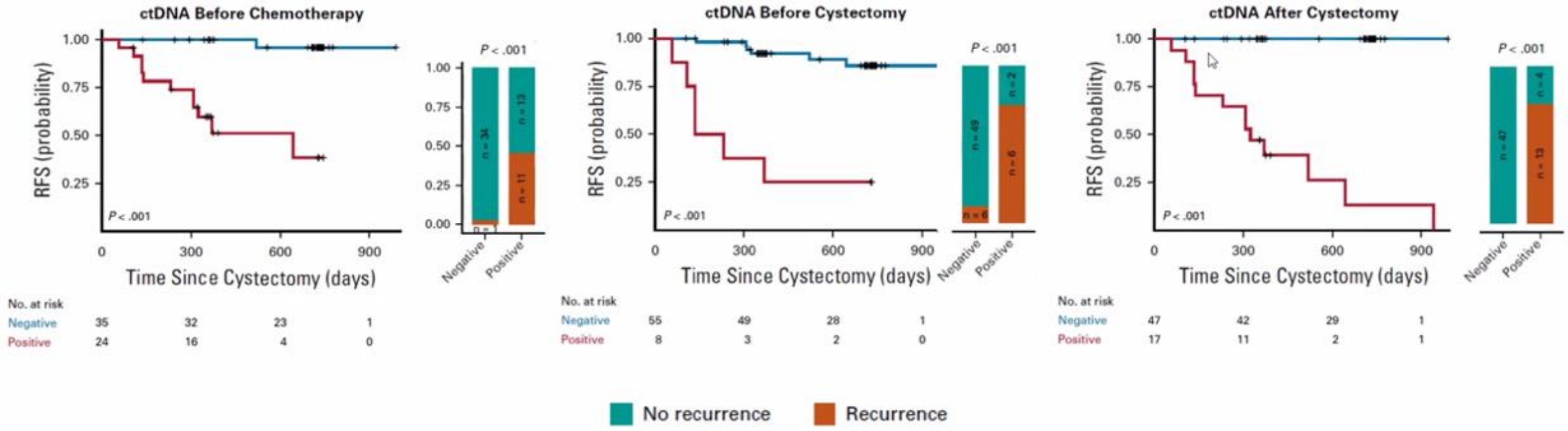
Longitudinal ctDNA analysis in MIBC



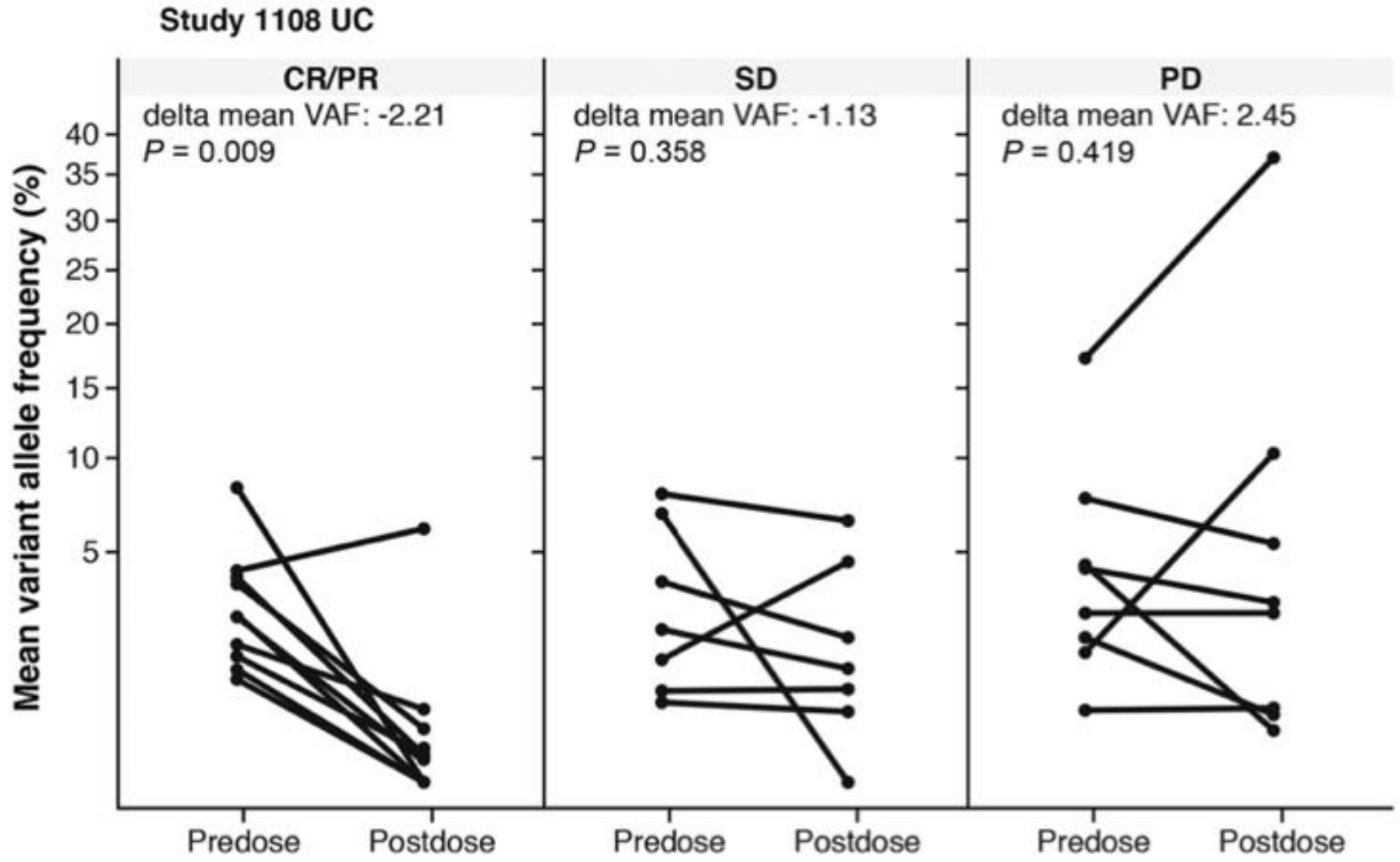
68 patients

Christensen et al., JCO, 2019

Correlation between ctDNA and NAC in MIBC



Correlation between ctDNA and IO in mUC

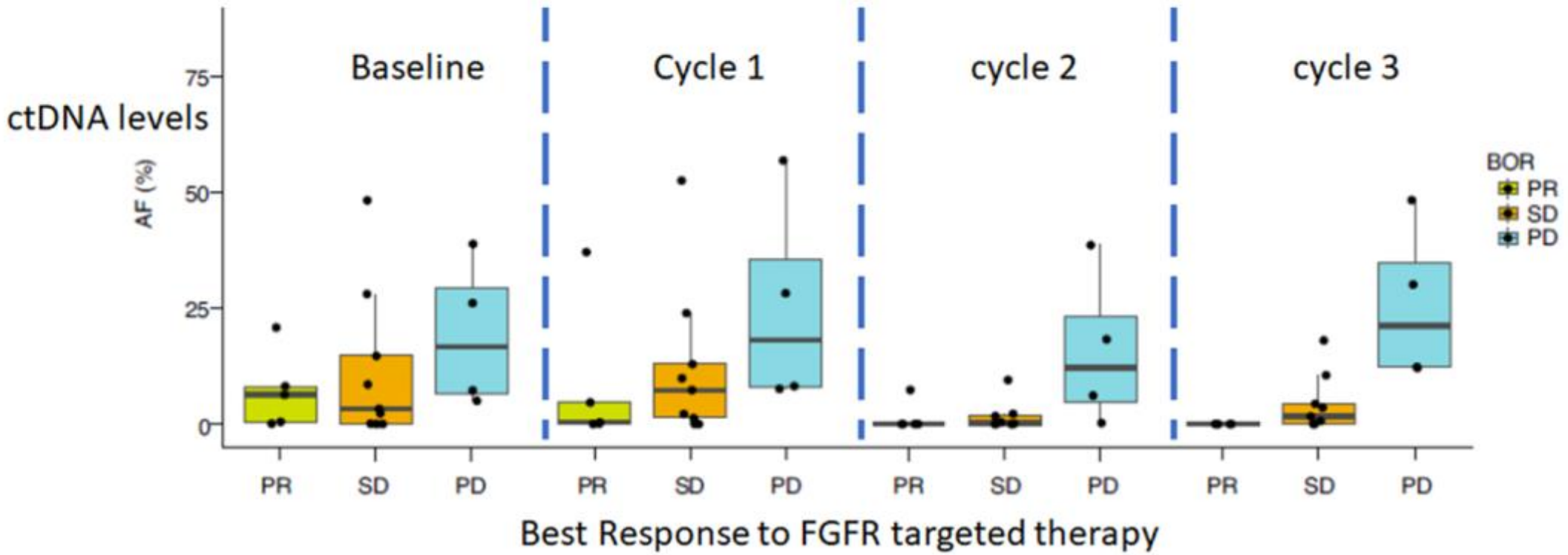


Raja et al., Clin Cancer Res 2019

nature medicine
LETTERS
https://doi.org/10.1038/s41591-021-01317-6

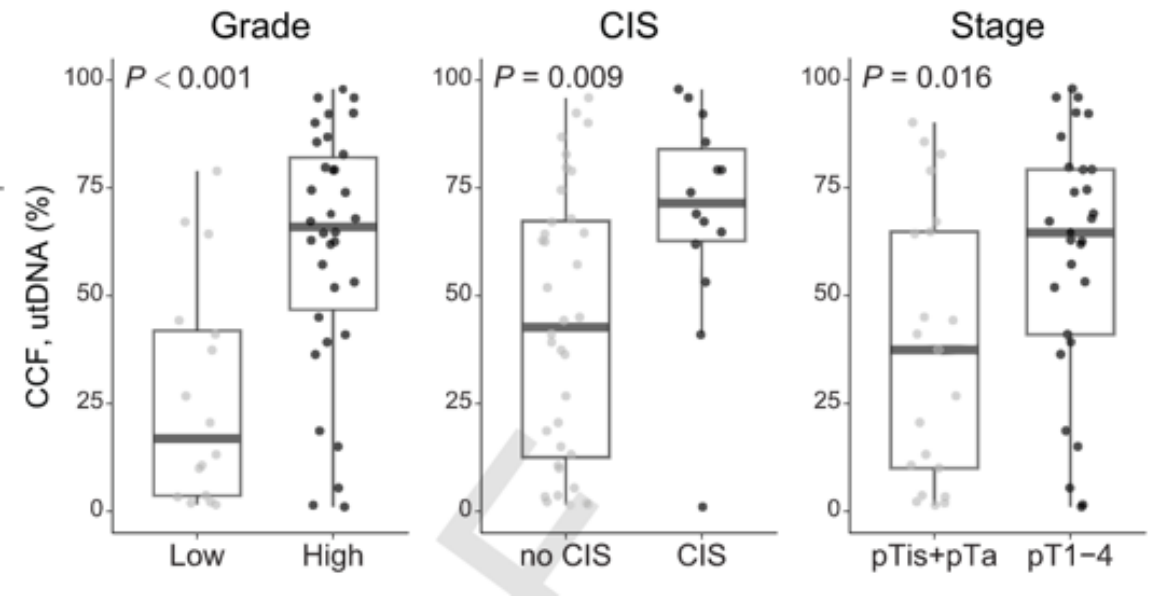
An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer

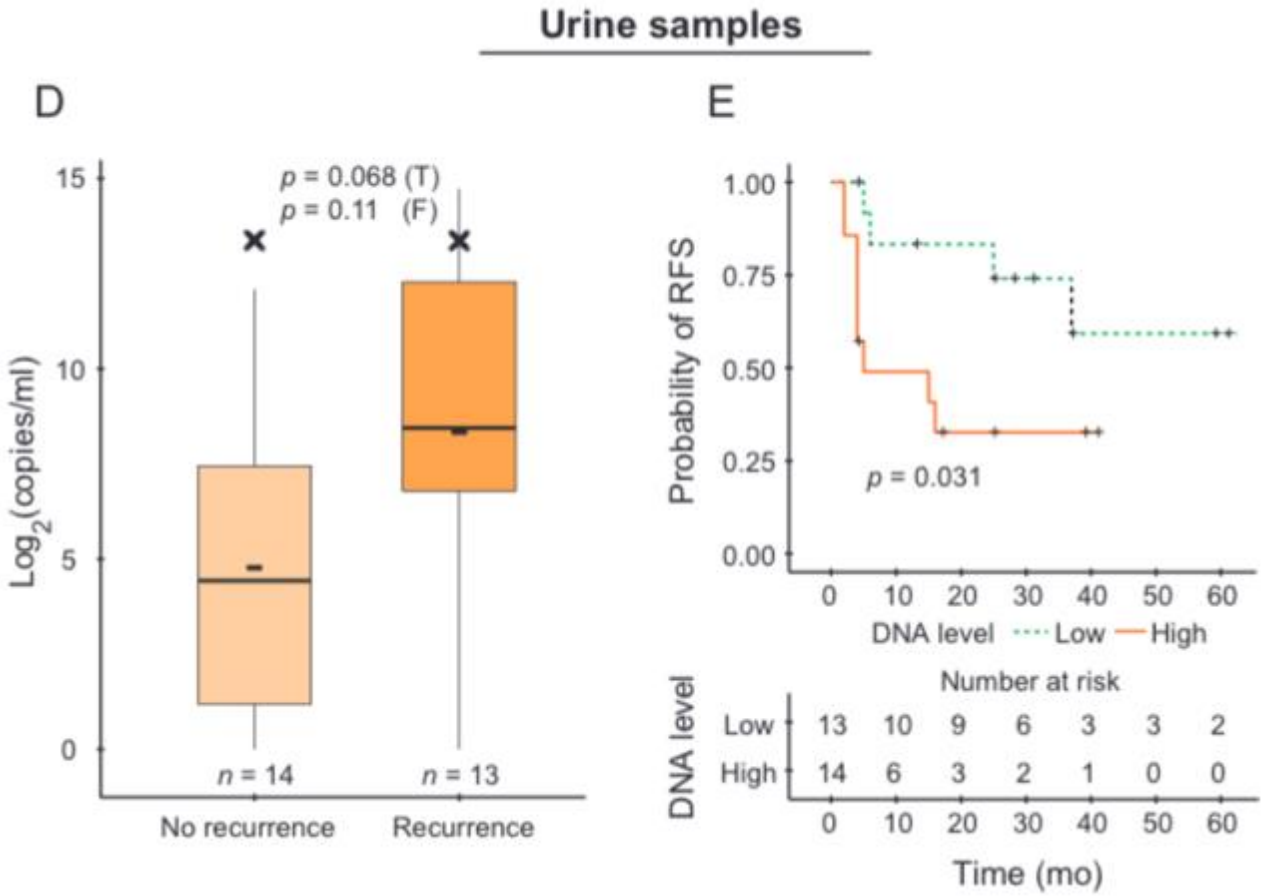
Response to FGFR targeted therapy correlating with changes to tracked FGFR mutations



Powles et al., Nat Med, 2021

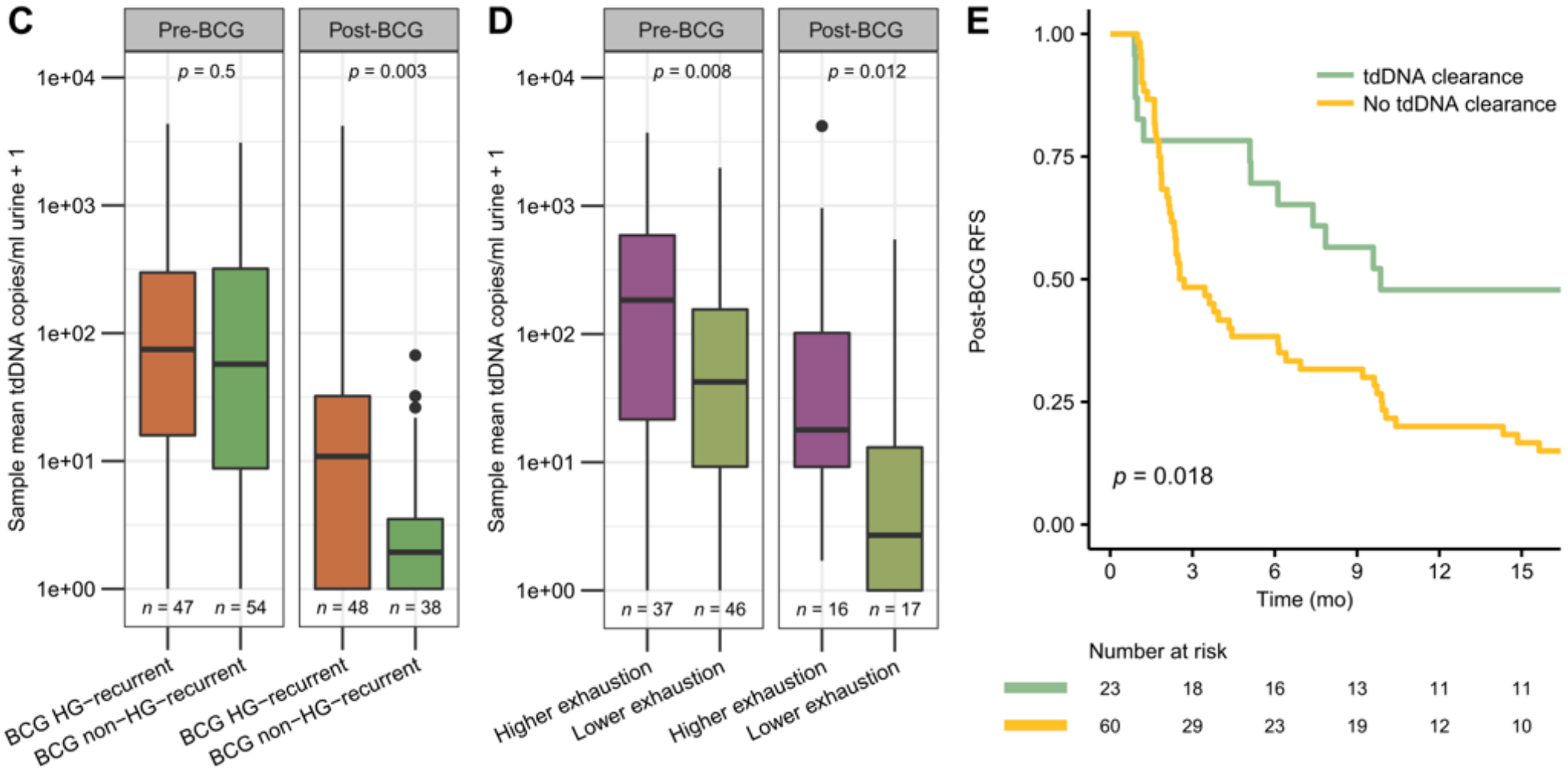
Urinary tumour DNA (utDNA)





Zhang et al., J Urol, 2021, Christensen et al., Eur Urol 2017

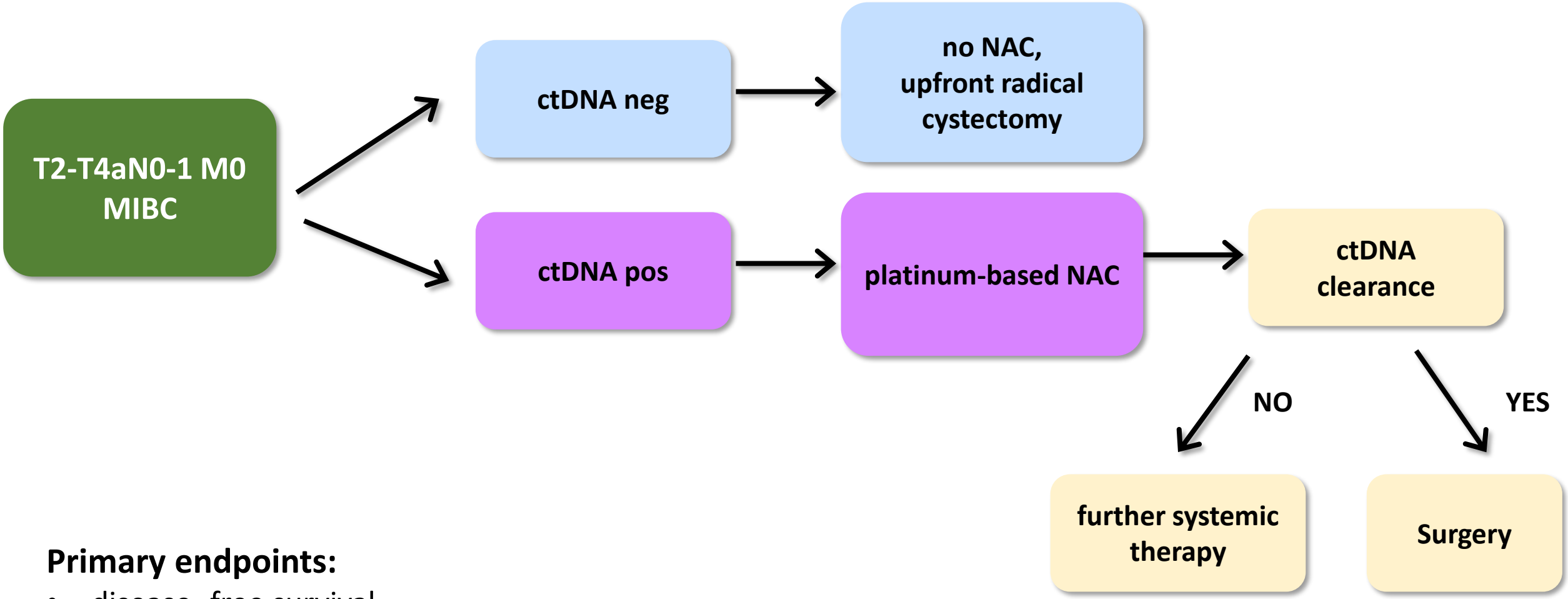
Post-BCG utDNA persistence identifies patients at high risk of recurrence in NMIBC



Strandgaard et al., Eur Urol 2022

Use in clinical trials

ctDNA guided treatment in the NEOADJUVANT setting

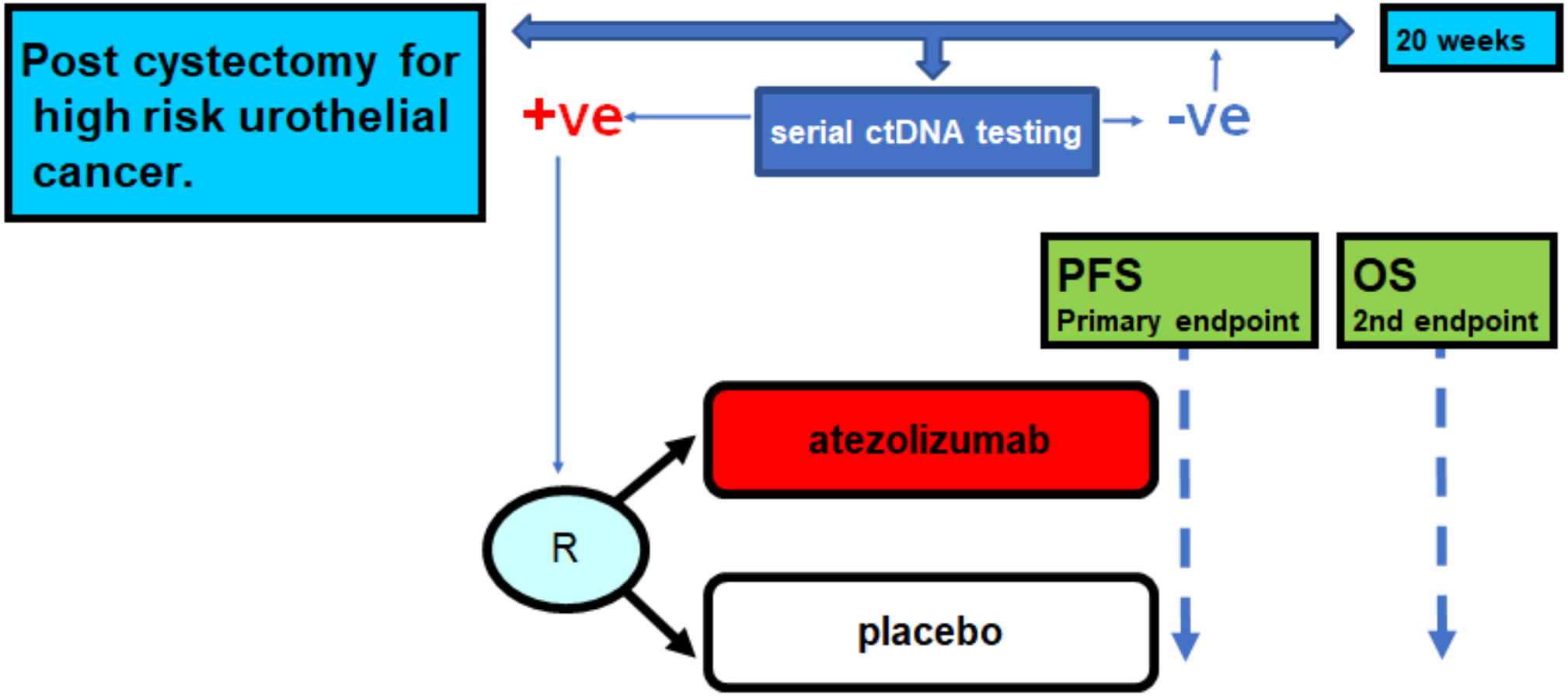


Primary endpoints:

- disease- free survival
- cystectomy-free survival

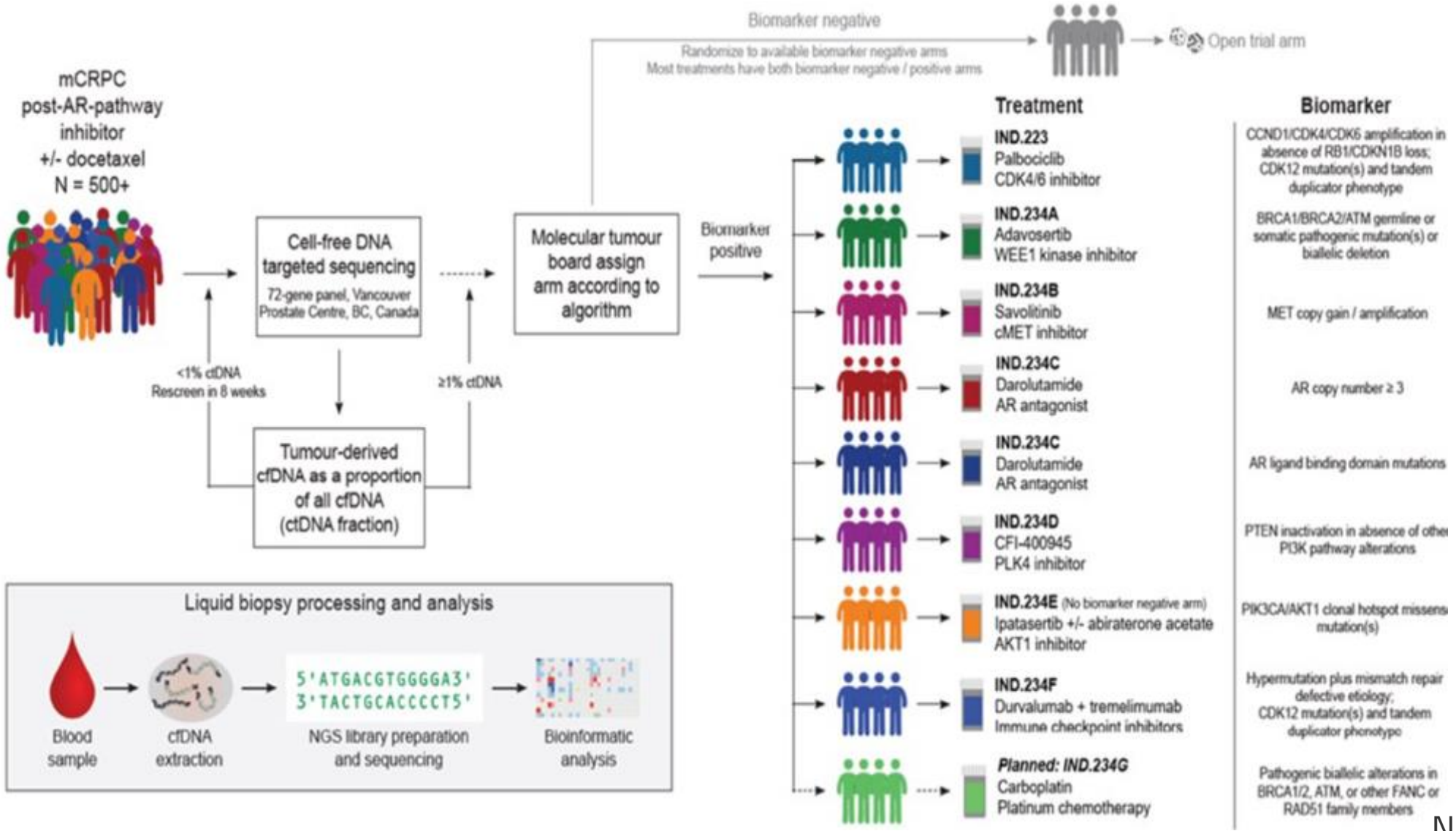
ctDNA guided treatment in the ADJUVANT setting

Adjuvant Atezolizumab vs Placebo in High-Risk Muscle-Invasive Bladder Cancer Who Are ctDNA Positive Following Cystectomy (IMvigor011)



NCT04660344

ctDNA guided treatment in the METASTATIC setting



NCT03385655

Summary

- Novel technologies (Signatera, FoundationOne Tracker) enabling wider implementation of ctDNA analysis
- Useful during the entire disease course to inform clinical practice (MRD, response monitoring)

Need for prospective, ctDNA guided, adaptive clinical trials