IV GO NORTE INTERNATIONAL GU DEBATES
OCTOBER 2nd - 3rd 2025
#GonorteGUDebates

The role of ctDNA to decide postoperative treatment in MIBC: are we ready for prime time?

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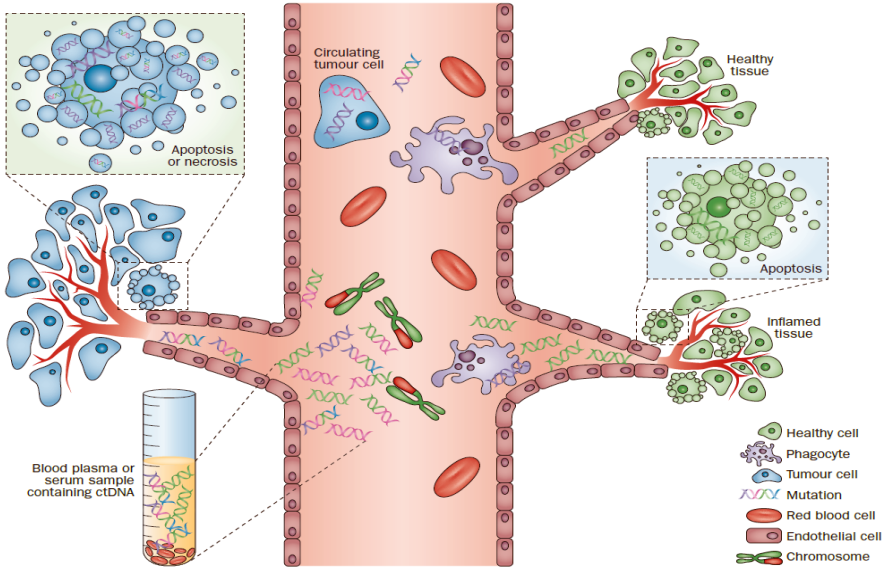
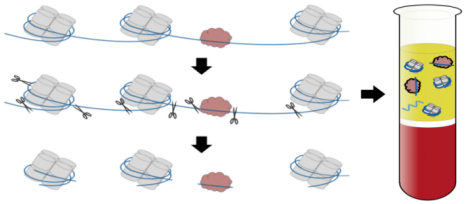
Department of Urology; Mount Sinai Icahn School of Medicine, Elmhurst/Queens Hospitals

What is ctDNA?





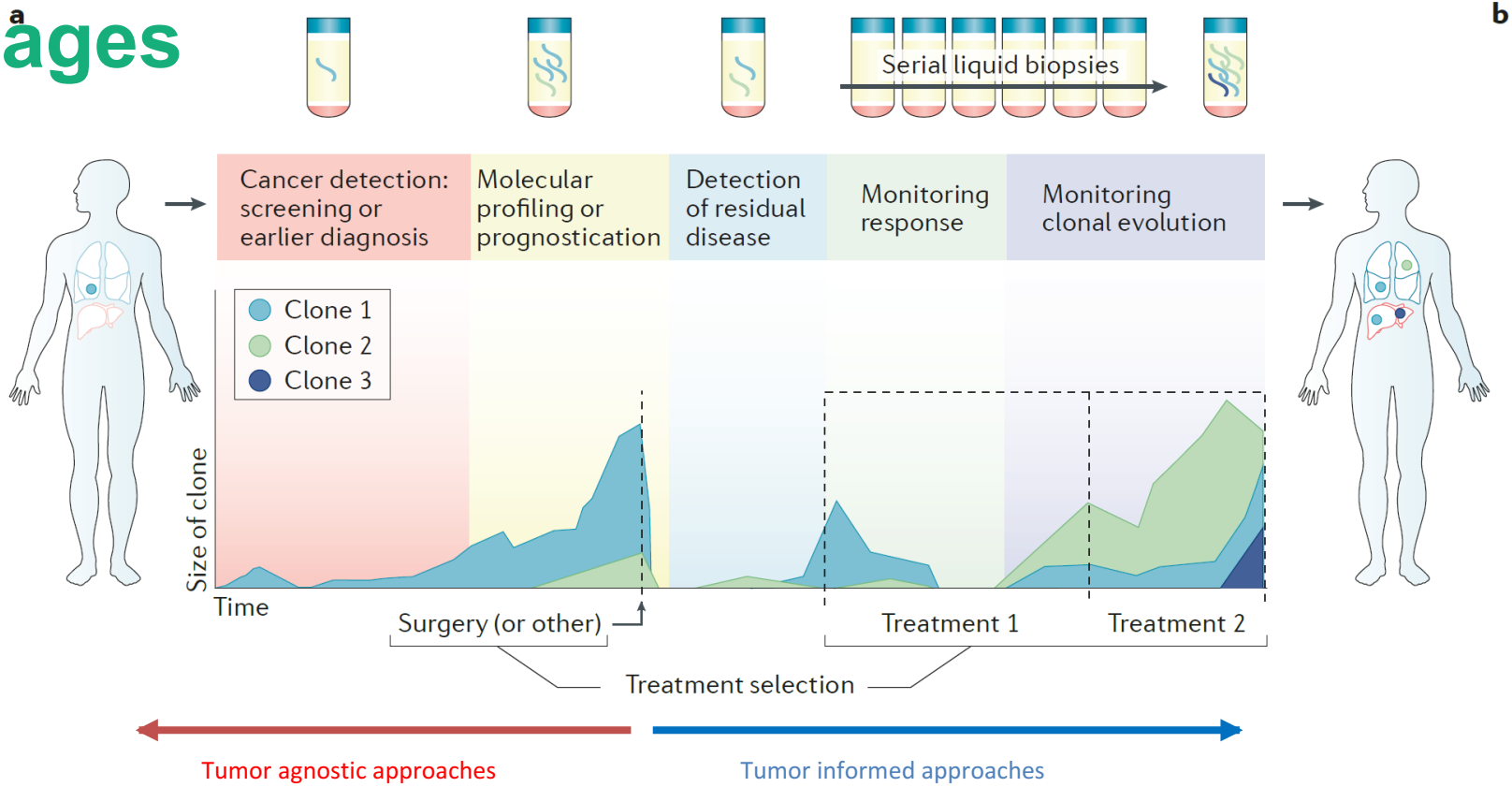
DNA fragments (<146bp)

Urine cfDNA
from renal clearance

cfDNA half life: <2 hours → real time monitoring of tumor burden

Leary et al, Sci Transl Med, 2012; Crowley et al., Nature Reviews Clinical Oncology, 2013; Corcoran et al., New England Journal of Medicine, 2018

ctDNA has potential to be used thru disease stages

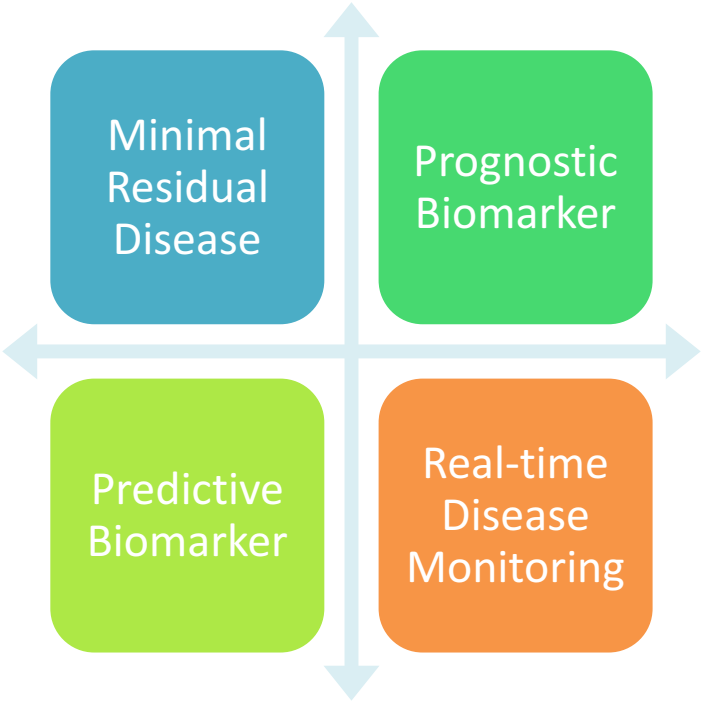


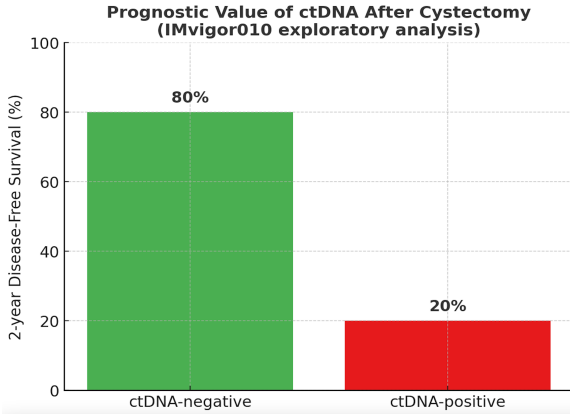
Wan et al., Nat Review Cancer 2017

Why is ctDNA important as a Biomarker in Urothelial Carcinoma?

IMvigor 010

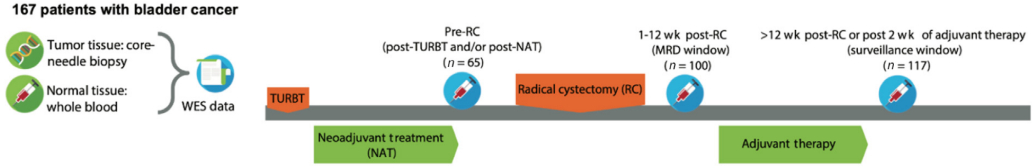
IMVigor 011
MODERN
TOMBOLA

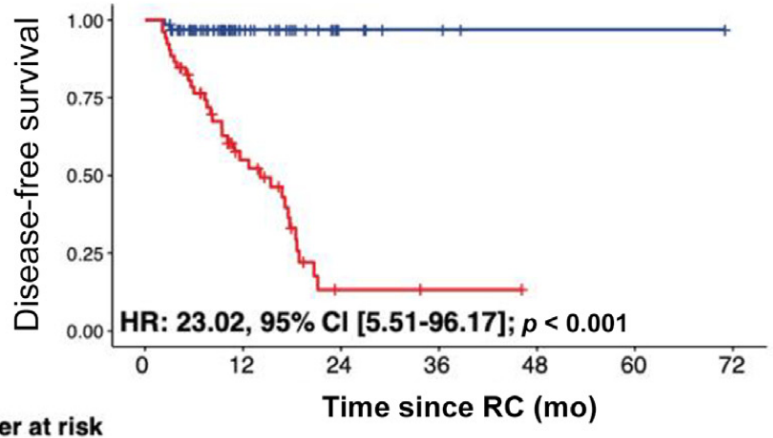




ctDNA Assessment → Risk Stratification

- ✓ Strong association between ctDNA detectability and poor DFS
- ✓ **ctDNA status is better predictor of DFS than pCR**





Number at risk

ctDNA undetectable	65	24	6	3	1	1	0
ctDNA detectable	52	20	2	1	0	0	0

Status	ctDNA undetectable	ctDNA detectable
Events %	3.1 (2/65)	63.5 (33/52)
24-mo DFS %	96.9 (88.2-99.2)	13.2 (3.8-28.6)

Association of Tumor-informed Circulating Tumor DNA Detectability Before and After Radical Cystectomy with Disease-free Survival in Patients with Bladder Cancer

John P. Sfakianos [a,†], Arnab Basu [b,†], George Laliotis [c], Shivaram Cumarasamy [a], Jordan M. Rich [a], Ajitha Kommalapati [b], Michael Glover [d], Tamara Mahmood [c], Neeraja Tillu [a], Christopher J. Hoimes [e], Grayce Selig [e], Revathi Kollipara [f], Tyler F. Stewart [g], Samuel Rivero-Hinojosa [c], Punashi Dutta [c], Mark Calhoun [c], Shruti Sharma [c], Meenakshi Malhotra [c], Adam C. ElNaggar [c], Minetta C. Liu [c], James E. Ferguson 3rd [b], Marcio Diniz [h], Reza Mehrazin [h], Peter Wiklund [a], Alan Tan [f], Sumit Shah [d], Matthew D. Galsky [h,]*

Limitations of ctDNA

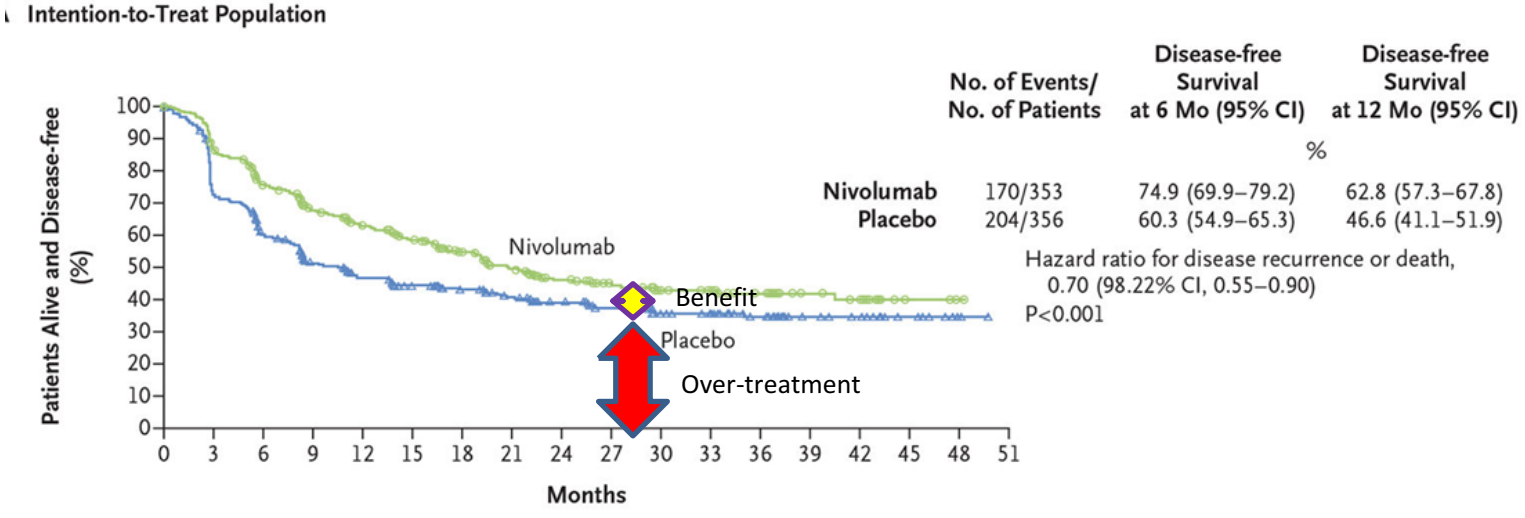
1. Sensitivity depends on tumor fraction (low shedding in some NMIBC, small-volume, or papillary disease)- MDR??

2. Standardization of assays is lacking (different panels, thresholds, platforms)- **Tumor informed ctDNA assays vs non-tumor informed ctDNA**

3. Not yet fully integrated into guidelines — but rapidly moving toward clinical implementation. IMvigor 011?

ctDNA to guide Adjuvant Therapy

Adjuvant IO For high-Risk TCC- Pathological Definition/Imaging, EU



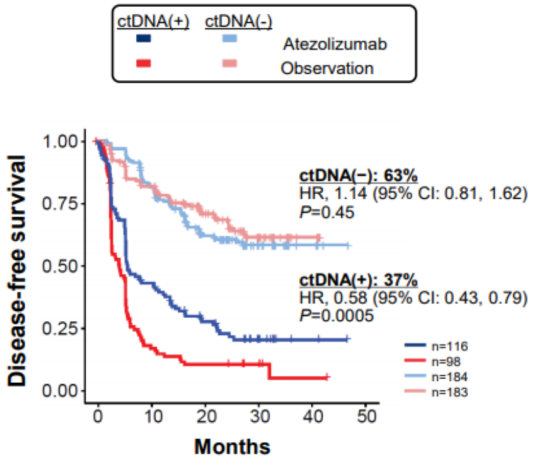
	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

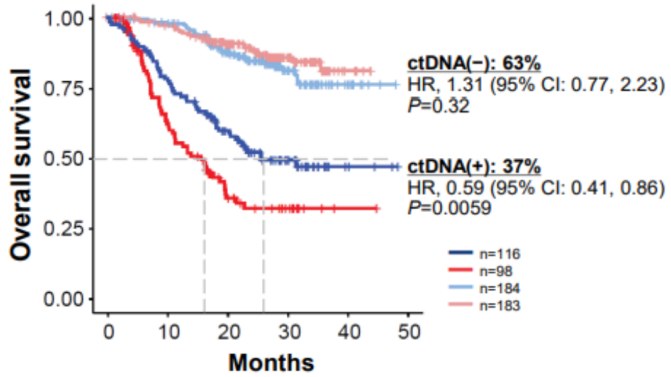
Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

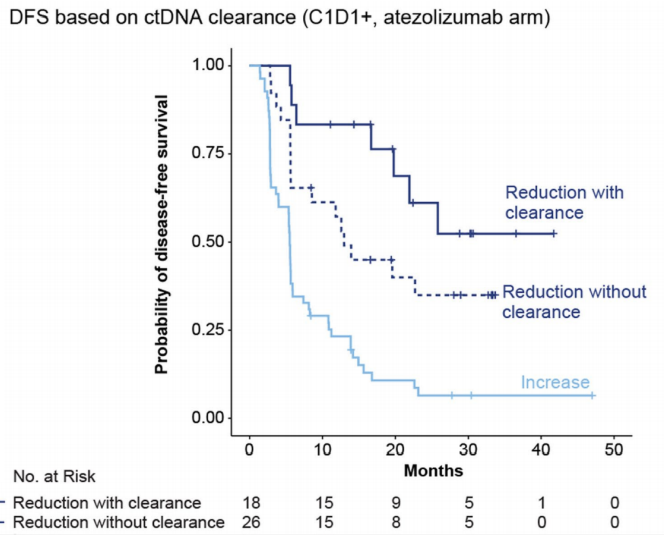
CM-274 (nivolumab)	Ambassador (Pembrolizumab)	Imvigor 010 (Atezolizumab)
• DFS • OS trending	• DFS	• NO DFS/OS

Bajorin et al NEJM 2021

ctDNA prognostic/predictive of OS w/ adjuvant atezolizumab- Imvigor 010



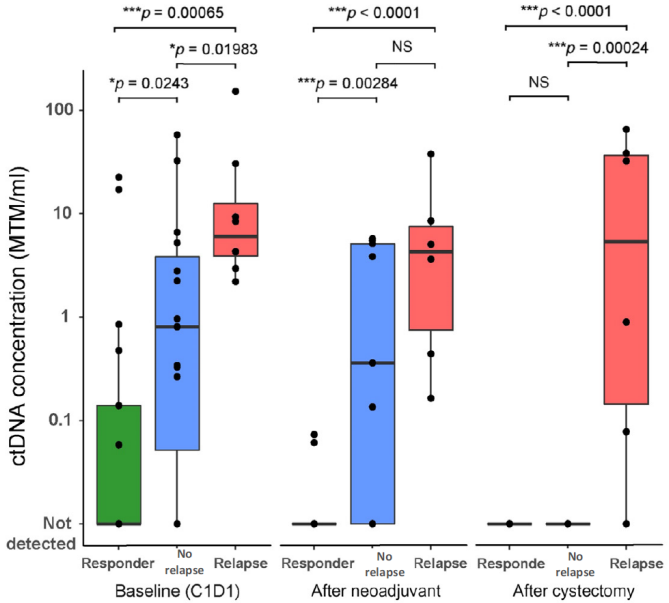


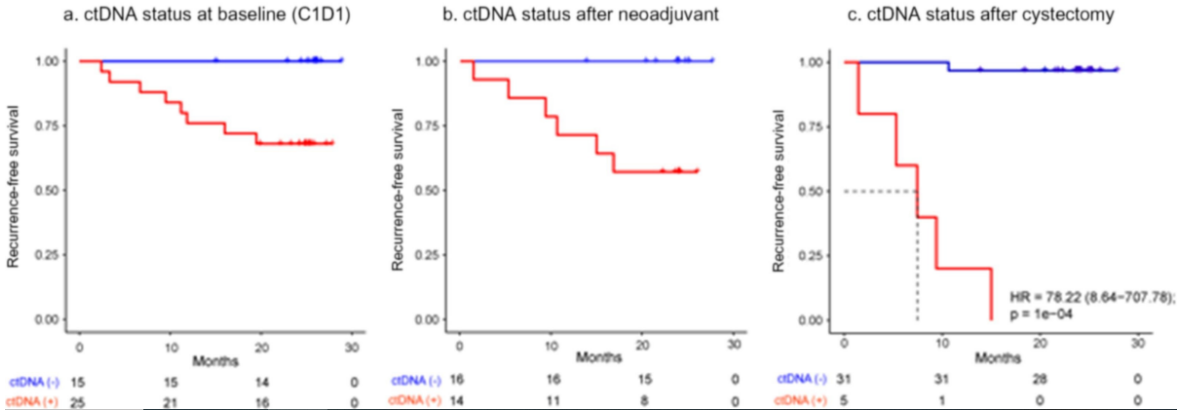


	ctDNA(+) patients	
	Atezolizumab	Observation
Median DFS (95% CI), mo	5.9 (5.6, 11.2)	4.4 (2.9, 5.6)
Median OS (95% CI), mo	25.8 (20.5, NR)	15.8 (10.5, 19.7)

Powles et al., Nature. 2021

ctDNA prognostic in ABACUS Trial→ Neoadjuvant Atezolizumab

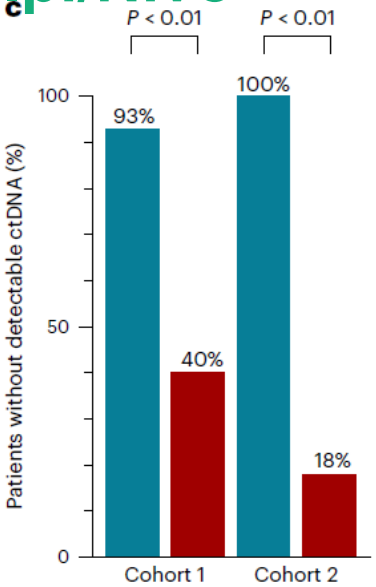




Szabados et al, European Urology, 2022

ctDNA Dynamics in NABUCCO Trial→ Neoadjuvant Ipi/Nivo

c

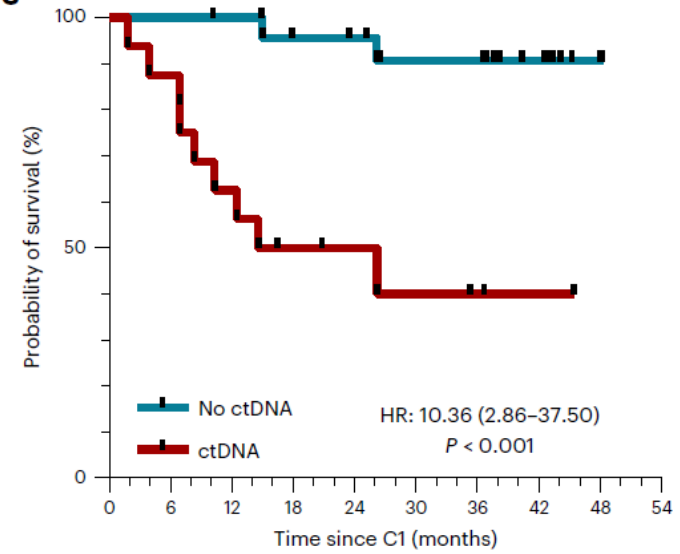


d

	No detectable ctDNA, *n*	Detectable ctDNA, *n*	Total, *n*
Cohort 1, *n*			
Responders	13	1	14
Non-resp.	4	6	10
Total	17	7	24
Cohort 2, *n*			
Responders	5	0	5
Non-resp.	2	9	11
Total	7	9	16

Legend Fig. 2a–c
ypT0/Tis/Ta/T1N0 ≥ypT2 or N+ Non-evaluable

e

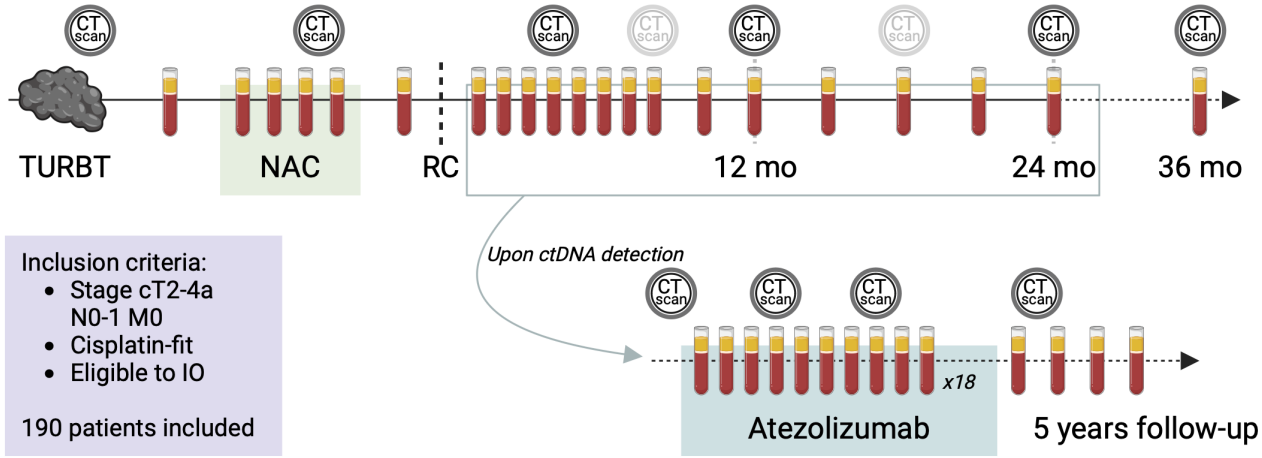


at risk

No ctDNA	25	25	24	21	20	16	16	8	1	0
ctDNA	16	14	10	6	5	4	3	3	0	0

van Dorp et al., Nature Medicine 2023

TOMBOLA Trial→ ctDNA Guided intervention Trial in MIBC



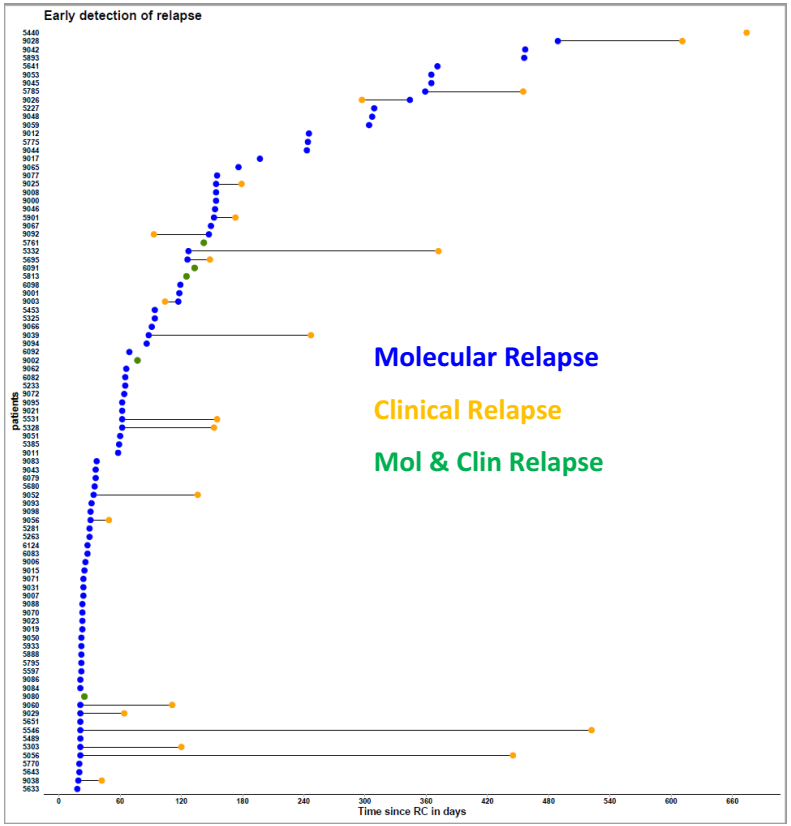
Inclusion criteria:
- Stage cT2-4a N0-1 M0
- Cisplatin-fit
- Eligible to IO

190 patients included

Primary objective:

- Complete response (CR) after treatment with investigational agent initiated by ctDNA positive status after radical cystectomy.

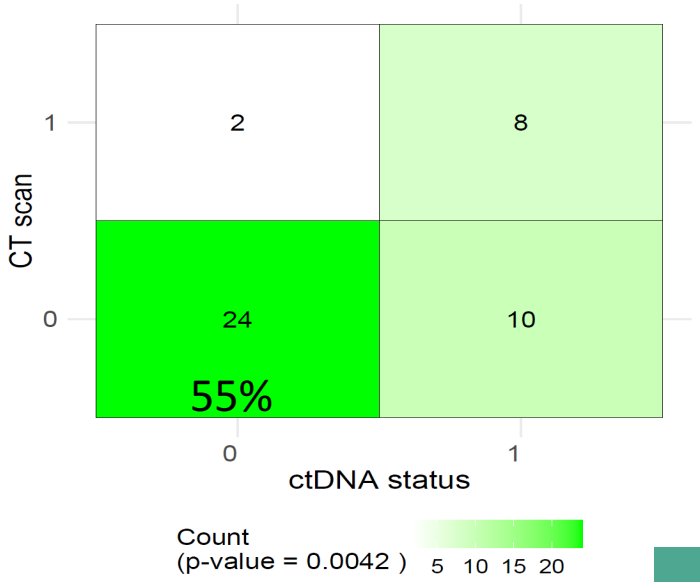
CR defined as NED - negative ctDNA and no visible metastasis on CT

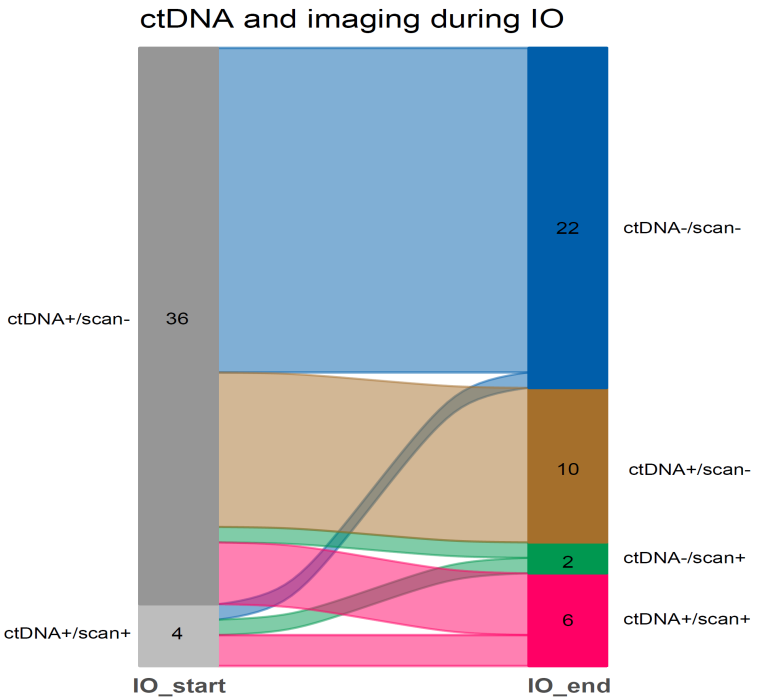


- ✓ 93 of 166 patients (56%) were ctDNA+ post-RC
- ✓ 75% were detected < 4 months post RC
- ✓ Of the ctDNA- patients, only 2 (3%) developed metastases on CT-scan during follow-up

NED (No evidense of disease) (CT and ctDNA-)

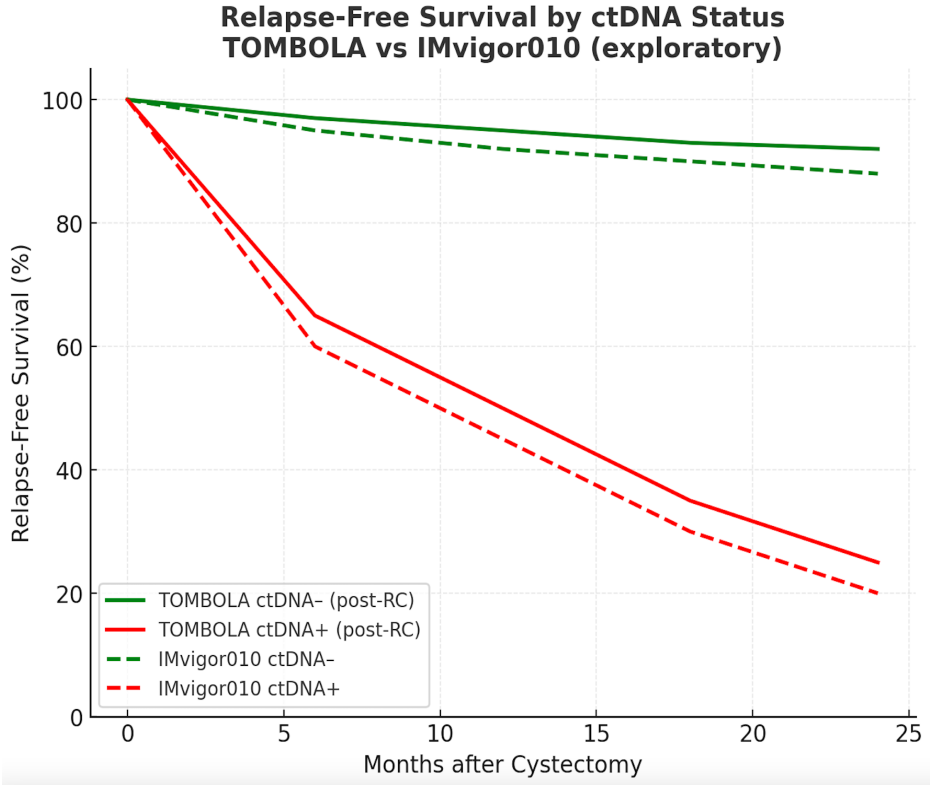
following immunotherapy





Serial measurements of ctDNA following NAC and RC is a highly specific method to identify patients that might benefit from early immunotherapy at a time of minimal metastatic disease

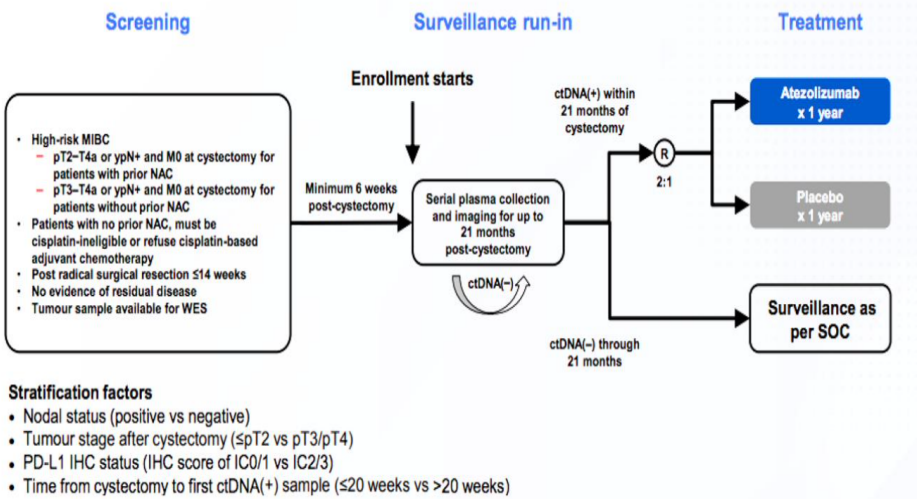
Jørgen Bjerggaard Jensen ESMO 24



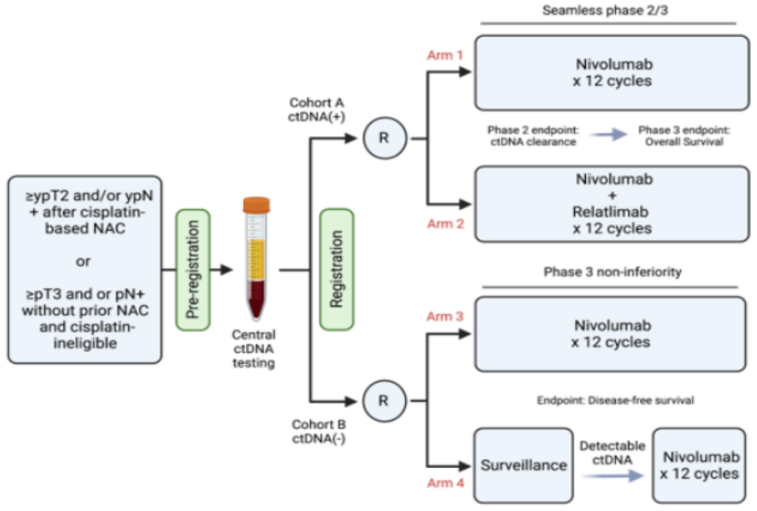
- **Prognostic power**
- **Lead Time to intervention**
- **Potential to guide adjuvant therapy**

ctDNA-guided Adjuvant IO Trials

IMvigor011- ctDNA positive pts randomized to atezo vs placebo

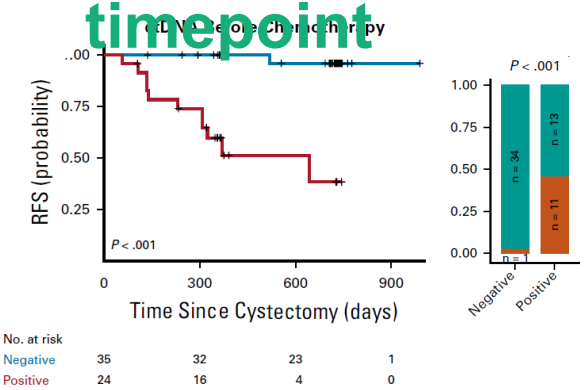


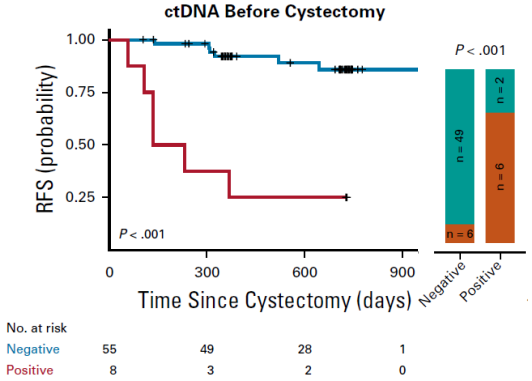
MODERN- pts randomized to immediate nivo vs when they become ctDNA positive

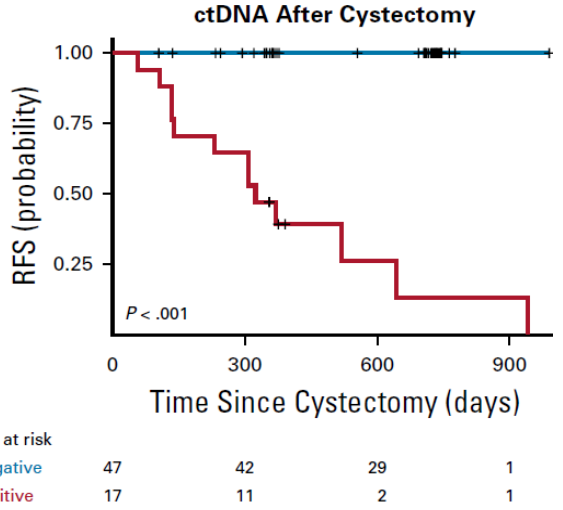


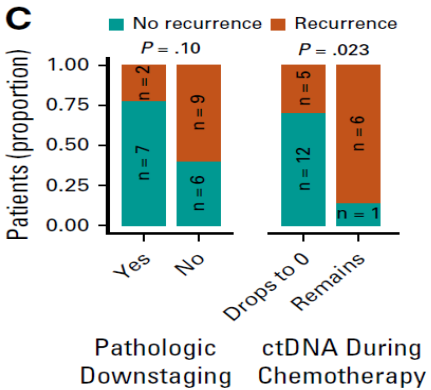
ctDNA to guide Bladder Preservation

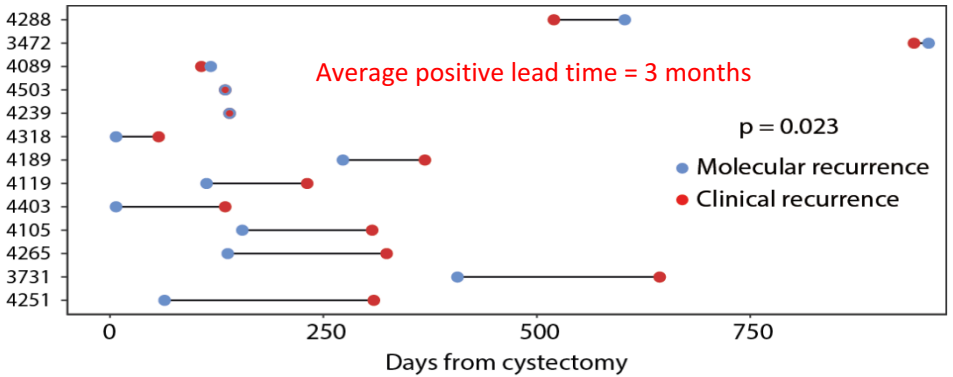
ctDNA is Prognostic of Recurrence in MIBC @ any timepoint





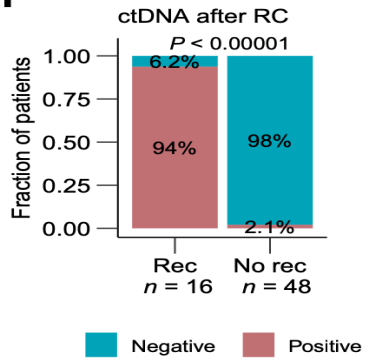


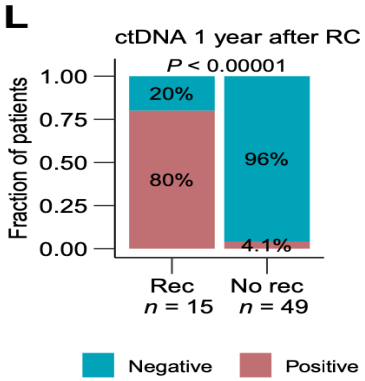


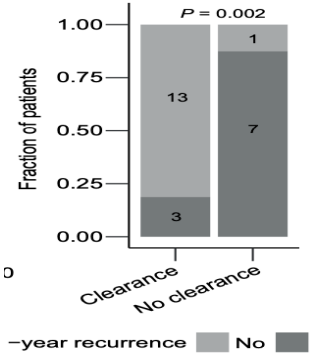


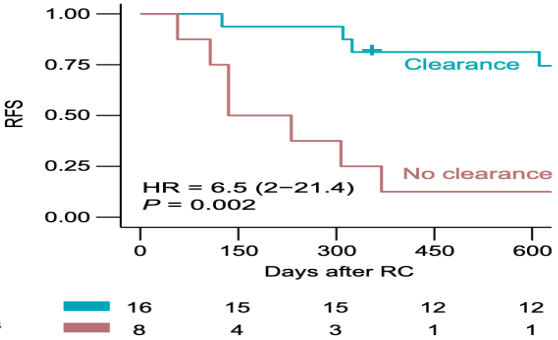
Christensen et al., J Clin Oncol. 2019

ctDNA Dynamics during NAC prognostic in MIBC









- ✓ N=68; FU 5yr- to predict treatment response w/ ctDNA and early detection of metastasis
- ✓ Includes non-High-risk cohort
- ✓ ctDNA after RC identifies Metastasic relapse (sensitivity 94%)
- ✓ ctDNA Dynamic during NAC are associated w/ pts outcomes
- ✓ **NPV ctDNA predict MRD 89% preNAC/80% preRC**

Lindskrog et al., Clinical Cancer Research, 2023

ctDNA and Outcome after NAC

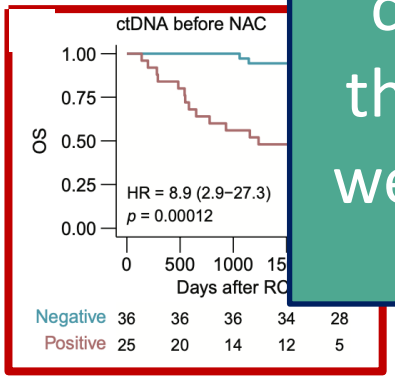
RESEARCH ARTICLE | OCTOBER 02 2023

Circulating tumor DNA analysis in advanced urothelial carcinoma: insights from biological analysis and extended clinical follow-up

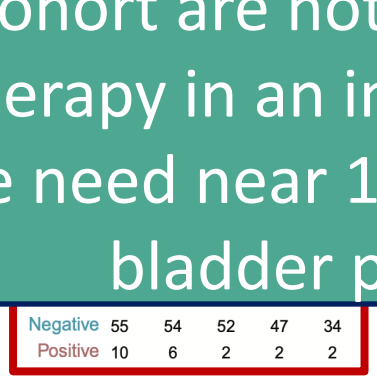
Sia V. Lindskrog ; Karin Birkenkamp-Demtroder ; Iver Nordentoft ; George Laliotis ; Philippe Lamy ; Emil Christensen ; Derrick Renner ; Tine G. Andreasen ; Naja Lange ; Shruti Sharma ; Adam C. ElNaggar ; Minetta C. Liu ; Himanshu Sethi ; Alexey Aleshin ; Mads Agerbæk ; Jørgen B. Jensen ; Lars Dyrskjøt

+ Author & Article Information

Clin Cancer Res (2023)



ctDNA negative : 89% ≤ypTa/CISN0



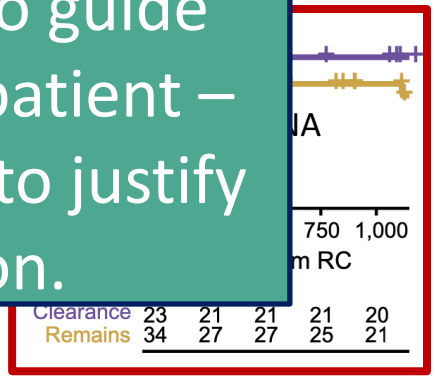
ctDNA negative : 80% ≤ypT1N0

(Signatera)

Correlations and associations in a cohort are not enough to guide therapy in an individual patient – we need near 100% NPV to justify bladder preservation.

Cell-Free Urine and Plasma DNA Mutational Analysis Predicts Neoadjuvant Chemotherapy Response and Outcome in Patients with Muscle-Invasive Bladder Cancer

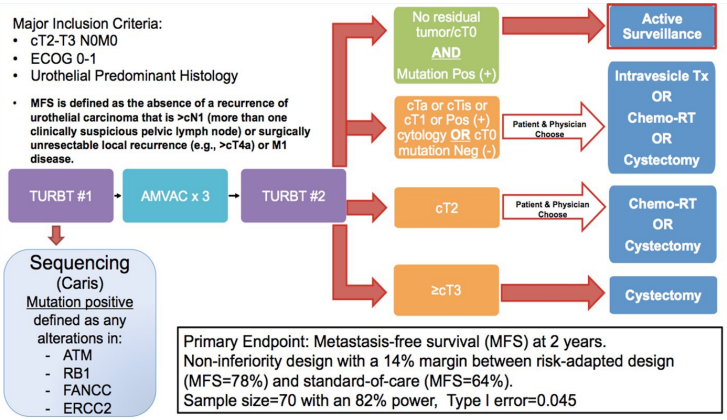
röder[1,2], Sara K. Elbæk[2], Sia V. Lindskrog[1,2], ael Knudsen[1], Philippe Lamy[1],



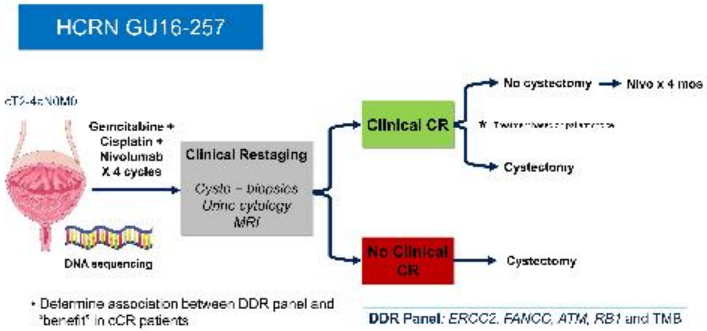
(Custom Panel)

All ctDNA positive patients had residual disease
All pCR were ctDNA negative

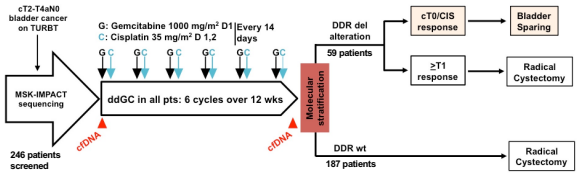
RETAIN Trial



HOOSIER



A031701: A phase II study of dose-dense Gemcitabine plus Cisplatin in patients with muscle-invasive bladder cancer with bladder preservation for those patients whose tumors harbor deleterious DNA damage response (DDR) gene alterations



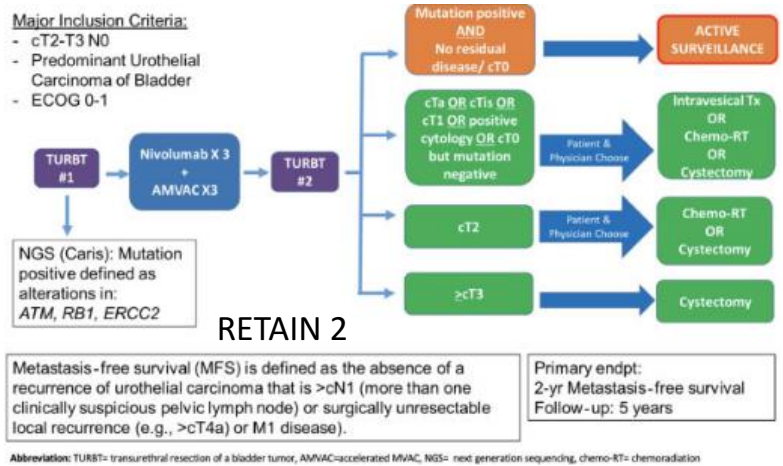
Modified DDR gene panel

ERCC2
ERCC5
BRCA1
BRCA2
RAD51C
ATR
RECQL4
ATM
FANCC

Deleterious alterations in one or more of these genes will allow patients to be potentially eligible for the bladder-sparing arm of the study

Alliance for Clinical Trials in Oncology

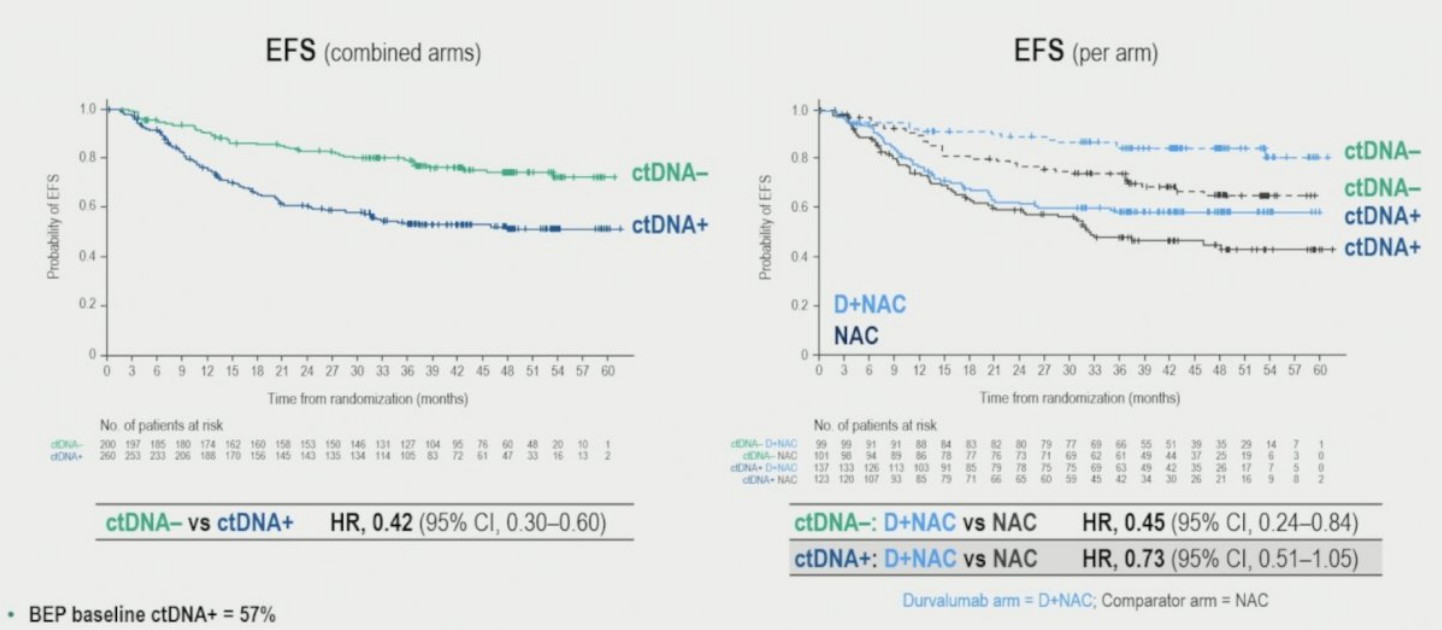
RETAIN 2



Gopa Iyer, MSKCC

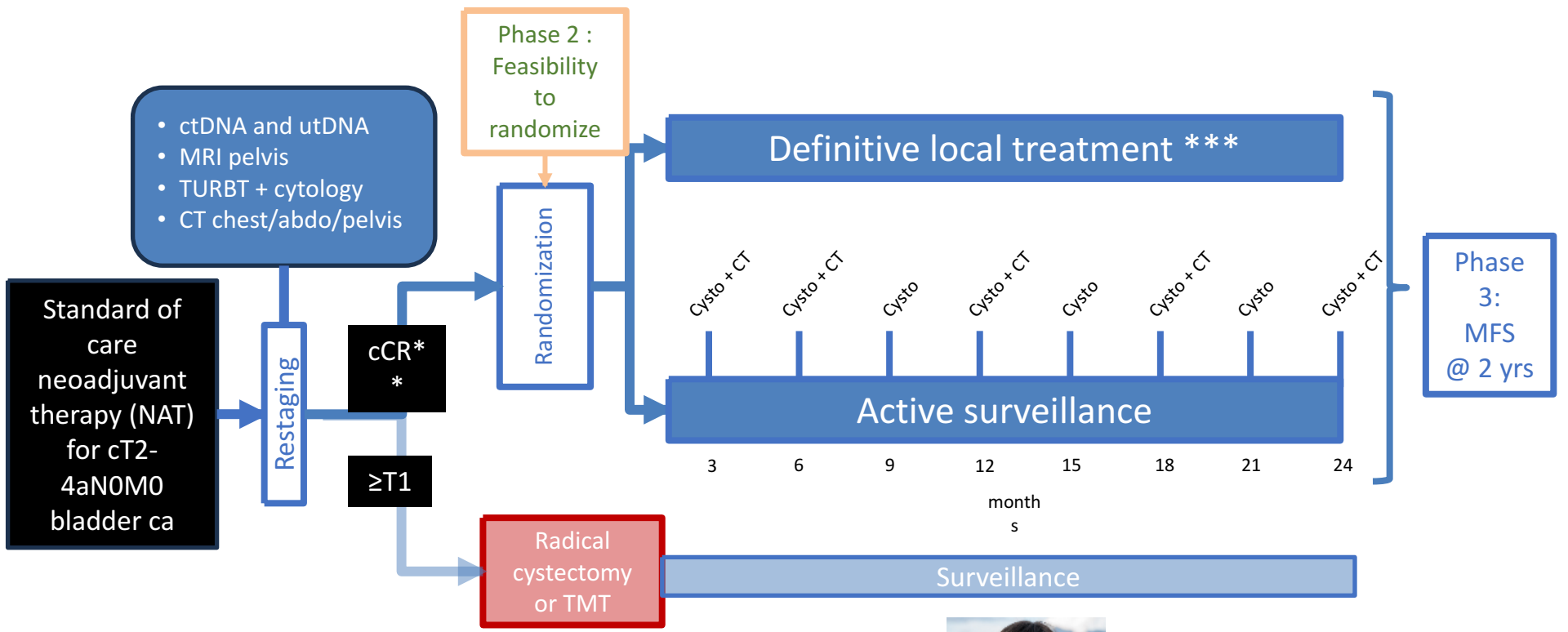
ctDNA to guide Perioperative Treatment

NIAGARA Trial- Durvalumab NAC



- ctDNA preRC correlated with no CR
- EFS Benefit if ctDNA clearance specially with D

Powles ASCO 2025



**Definition of cCR:

- Negative MRI (VI-RADS 0-1-2)
- Negative repeat TURBT (< cT1, no extensive CIS)
- Negative ctDNA
- Negative utDNA
- No mets (negative conventional CT or PET-CT)

Marie-Pier St-Laurent
UBC

*NAT = any SOC regimen approved at time of enrolment (Cisplatin, EV, IO, etc.)
*** Patient/investigator's choice; Radical cystectomy or TMT

Take Home Message→ ctDNA in MIBC

- ctDNA is the most promising tool we have to tailor adjuvant therapy in MIBC→ risk adapted adjuvant therapy.
- Current evidence shows **strong prognostic value** and signals of **predictive benefit** in guiding immunotherapy.
- But: **not ready for "prime time" yet** — still awaiting results from ongoing randomized ctDNA-guided trials (IMvigor 011 @ESMO 2025)
- Limitations apply → standardization assays; definition negative test; timing; costs

For now→ use in clinical trial settings, while preparing infrastructure for eventual adoption.