Dr. Arnav H. Tongaonkar

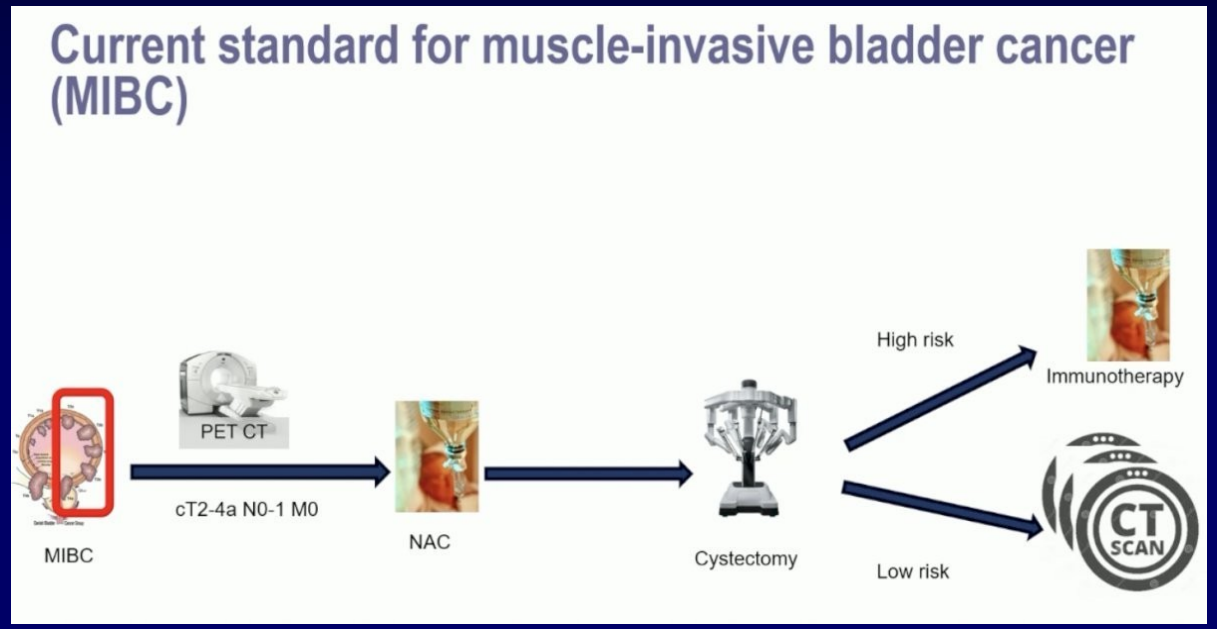
MD (Internal Medicine)
DM (Medical Oncology)
ECMO, MRCP (UK)
Certification in Immuno-Oncology (Harvard Medical School)

Identification of Bladder Cancer Patients That Could Benefit from Early Post- Cystectomy Immunotherapy Based on Serial Circulating Tumour DNA Testing: Preliminary Results from the TOMBOLA Trial

-Bjerggaard Jensen, K. Birkenkamp-Demtröder et al

M | O | C
Cancer Care & Research Centre

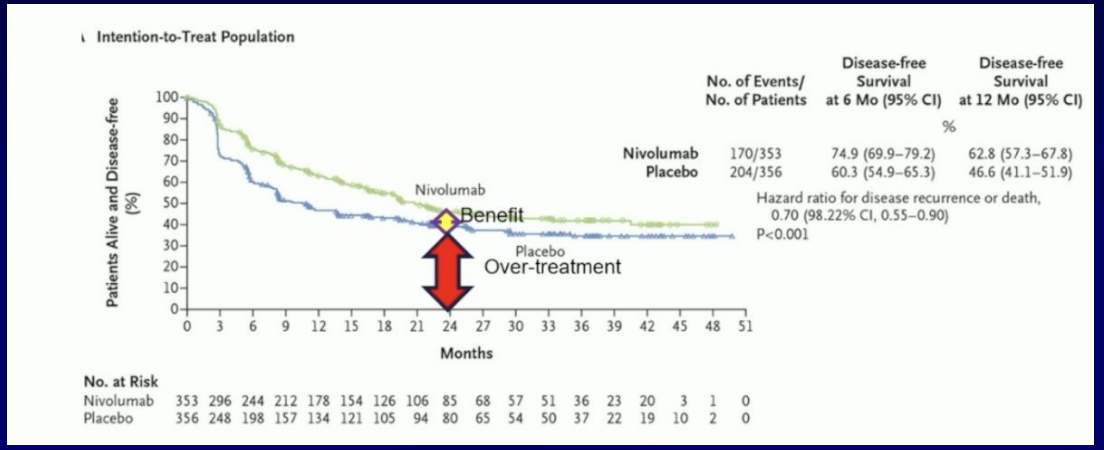
Introduction



- Current standard of care management option for muscle-invasive bladder cancer (MIBC) patients includes neoadjuvant chemotherapy followed by radical cystectomy
- High-risk patients receiving adjuvant immunotherapy based on high-risk pathologic features
- Low-risk patients undergoing serial surveillance using cross-sectional imaging, with systemic therapy reserved for recurrence.

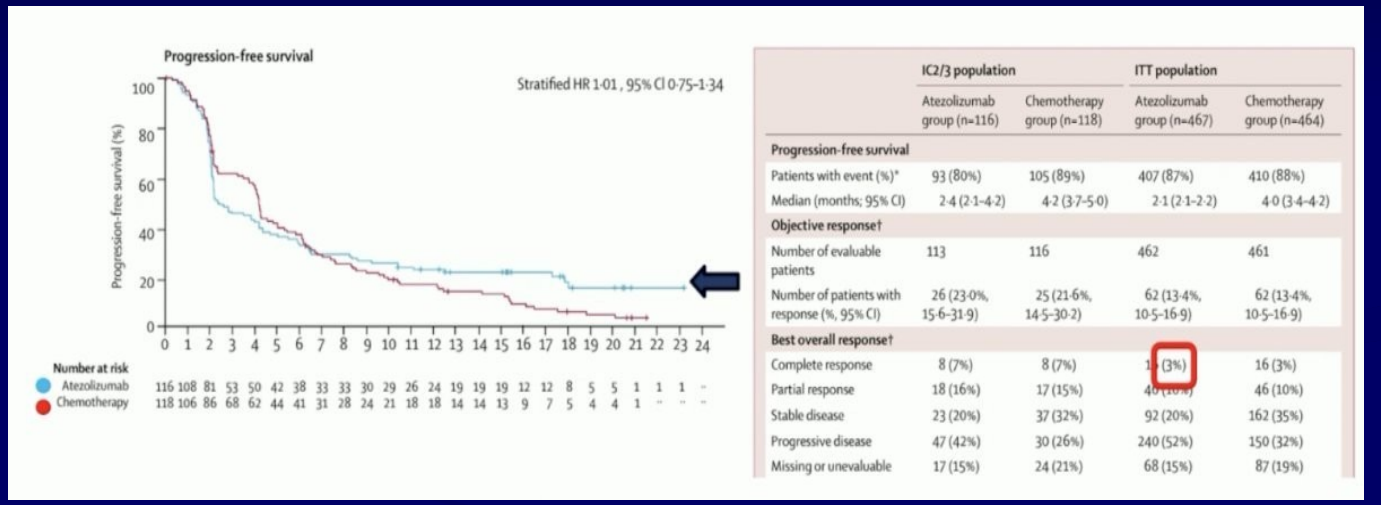
Adjuvant IO in high risk patients

- While there is evidence from phase III trials that adjuvant immunotherapy improves survival outcomes the authors commented that this absolute benefit is not clinically meaningful.
- Furthermore, as illustrated using the red arrow below, adjuvant therapy may represent overtreatment of the subset of patients that never recur.
- As such we must do better by avoiding overtreatment of ‘high-risk’ patients.



Treatment of low-risk patients with immunotherapy at the time of relapse

- Many patients with ‘low-risk’ disease cannot be salvaged with systemic immunotherapy at the time of clinical (i.e., imaging) recurrence.
- 80% of metastatic patients experiencing progression while on atezolizumab in the IMvigor211 trial, and only a 3% complete response rate achieved.

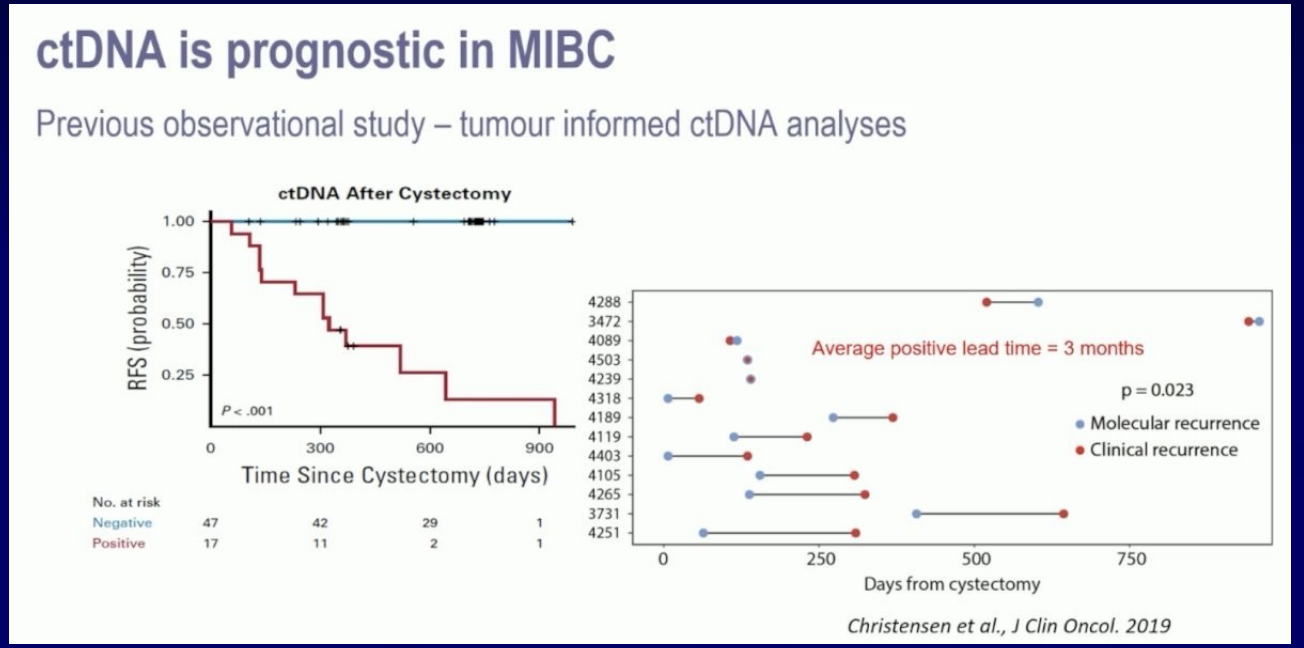


	IC2/3 population		ITT population	
	Atezolizumab group (n=116)	Chemotherapy group (n=118)	Atezolizumab group (n=467)	Chemotherapy group (n=464)
Progression-free survival				
Patients with event (%)*	93 (80%)	105 (89%)	407 (87%)	410 (88%)
Median (months; 95% CI)	2·4 (2·1–4·2)	4·2 (3·7–5·0)	2·1 (2·1–2·2)	4·0 (3·4–4·2)
Objective response†				
Number of evaluable patients	113	116	462	461
Number of patients with response (%, 95% CI)	26 (23·0%, 15·6–31·9)	25 (21·6%, 14·5–30·2)	62 (13·4%, 10·5–16·9)	62 (13·4%, 10·5–16·9)
Best overall response†				
Complete response	8 (7%)	8 (7%)	16 (3%)	16 (3%)
Partial response	18 (16%)	17 (15%)	46 (10%)	46 (10%)
Stable disease	23 (20%)	37 (32%)	92 (20%)	162 (35%)
Progressive disease	47 (42%)	30 (26%)	240 (52%)	150 (32%)
Missing or unevaluable	17 (15%)	24 (21%)	68 (15%)	87 (19%)

Accordingly, the study investigators asked the following question:
Can we avoid overtreatment of ‘high-risk’ patients and avoid delay of treatment in ‘low-risk’ MIBC patients by incorporating the use of ctDNA?

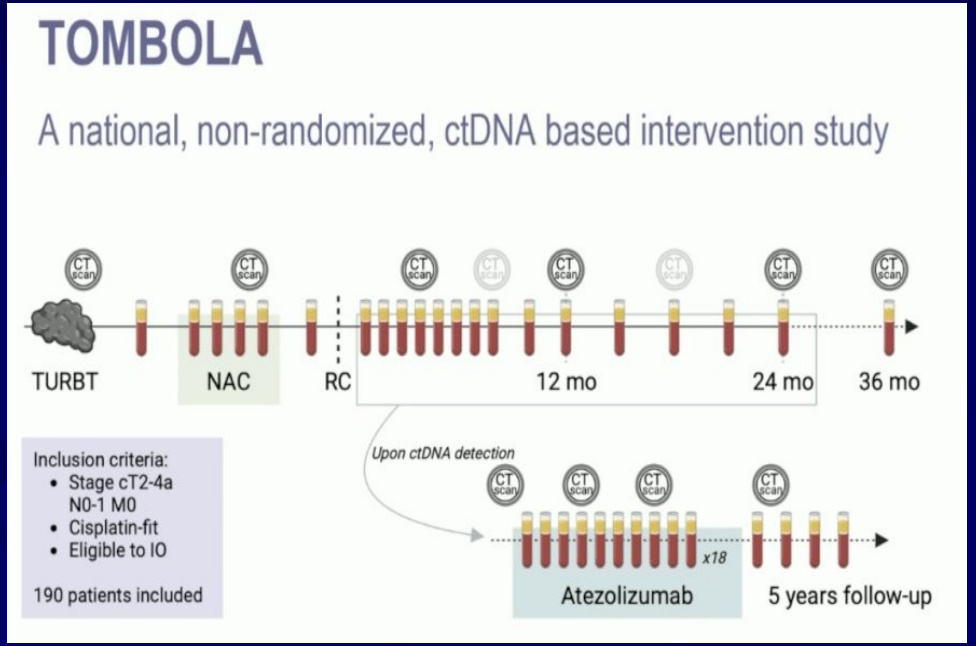
ctDNA Monitoring

- The study investigators have previously demonstrated that patients with a negative ctDNA status after radical cystectomy had a superior recurrence-free survival, compared to those with a positive ctDNA status.
- Furthermore, in patients who convert from a ctDNA negative to positive status, ctDNA had a three-month positive lead time, compared to cross-sectional imaging.



TOMBOLA- Trial design

- TOMBOLA was a national, non-randomized ctDNA-based intervention study conducted at 5 centers in Denmark.
- Eligible patients were those with cT2-4aN0-1M0, cisplatin, and immunotherapy-eligible MIBC who underwent NAC followed by radical cystectomy.
- Patients underwent serial ctDNA testing post-operatively.
- Upon ctDNA detection, patients were recommended for one year of atezolizumab therapy.



The primary objective was complete response after treatment with the investigational agent initiated by ctDNA positive status after radical cystectomy.

A complete response was defined by both a negative ctDNA status and no visible metastasis on CT.

The secondary objectives were:

- Duration of freedom from clinical relapse Overall survival
- Cancer-specific survival

The patient characteristics are summarized below. 39% and 61% of patients had clinical high- and low-risk disease.

Notably, among the clinical high-risk patients, 65% had a positive ctDNA status post-radical cystectomy. Conversely, almost half (49%) of the ‘low-risk’ patients were also ctDNA+ post-operatively.

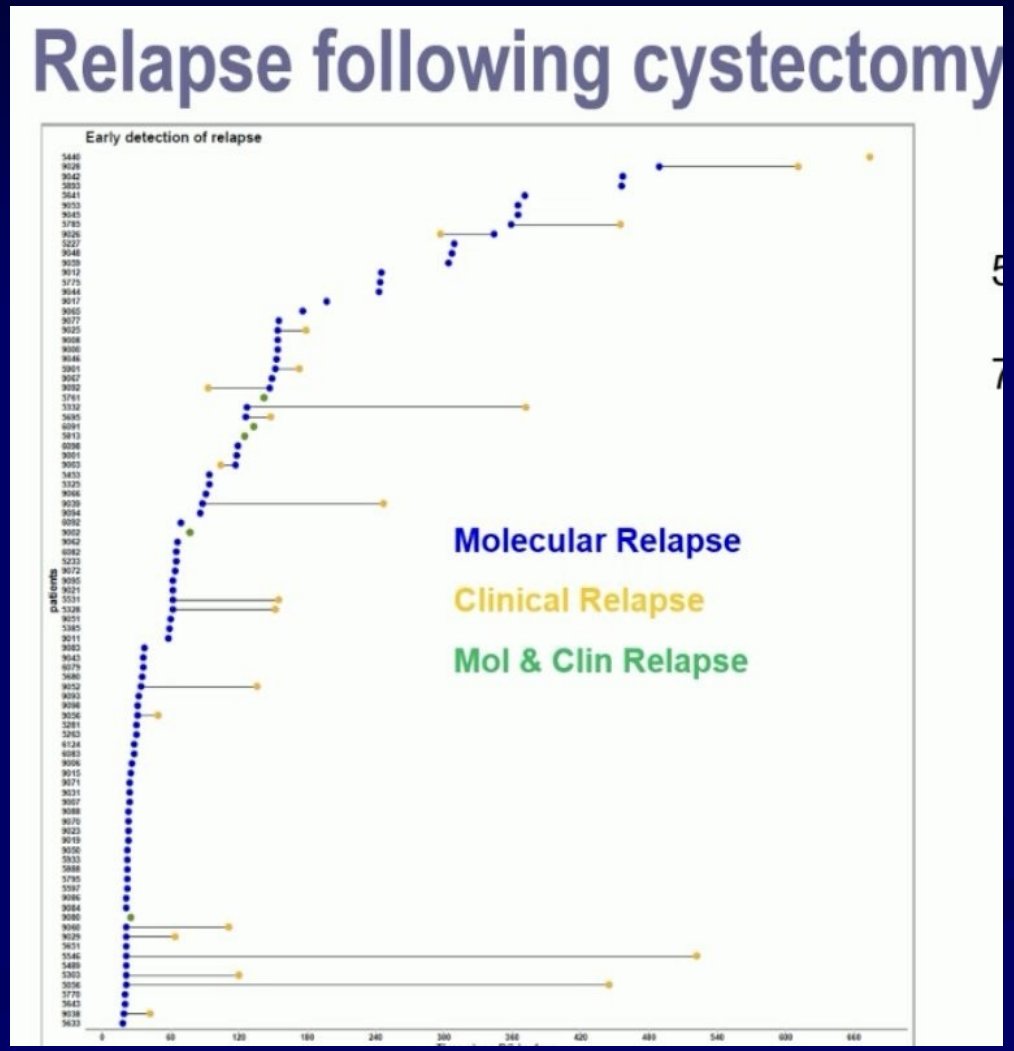
Variable	Patients, N = 179	ctDNA status post RC		p-value[1]
		Positive, N = 93	Negative, N = 73	
Age, Median (IQR)	65 (60, 71)	66 (61, 72)	63 (60, 70)	0.4
Sex, n (%)				0.2
Female	37 (21%)	16 (47%)	18 (53%)	
Male	142 (79%)	77 (58%)	55 (42%)	
T stage at RC, n (%)				0.003
T0	75 (42%)	33 (45%)	40 (55%)	
Ta-T1	27 (15%)	15 (56%)	12 (44%)	
T2	29 (16%)	15 (52%)	14 (48%)	
T3-T4a	37 (21%)	30 (81%)	7 (19%)	
*Tx**	11 (6.1%)	0 (NA%)	0 (NA%)	
N stage at RC, n (%)				0.12
N0	144 (80%)	75 (53%)	66 (47%)	
N1-N2	23 (13%)	17 (74%)	6 (26%)	
*Nx**	12 (6.7%)	1 (50%)	1 (50%)	
Clinical high risk, n (%)				0.044
Yes	69 (39%)	45 (65%)	24 (35%)	
*No***	110 (61%)	48 (49%)	49 (51%)	

exact test

Clinical high risk = pT2 or higher and/or N+ for patients treated with neoadjuvant chemotherapy. RC = Radical cystectomy. IQR = Interquartile range.* Missing information. ** For 13 patients, pT and/or pN status is missing.

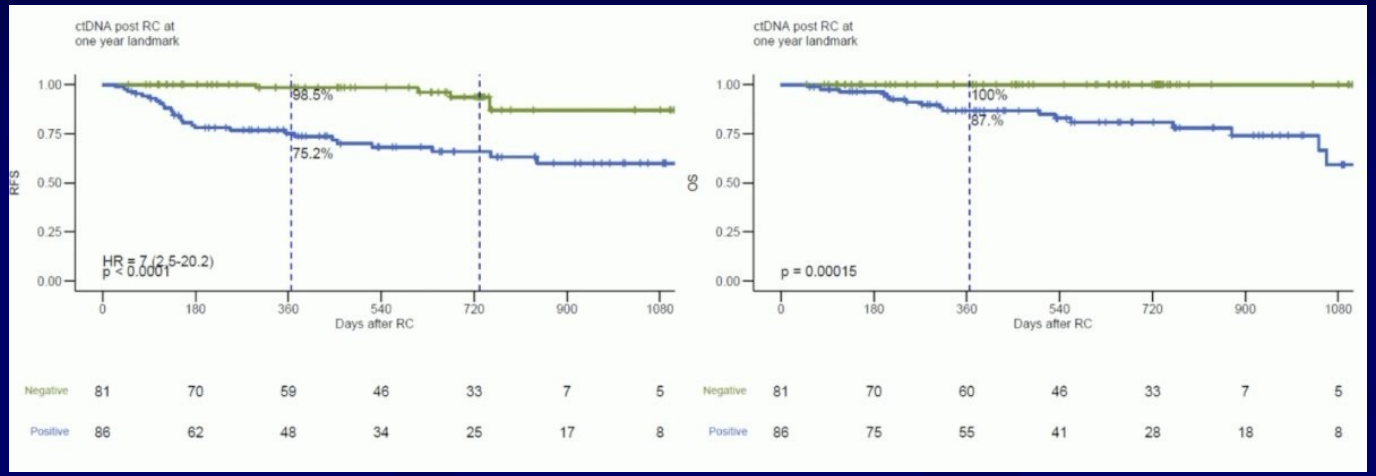
Results

- 56% of patients were ctDNA+ post-radical cystectomy. 75% were detected <4 months post-cystectomy.
- Of the ctDNA- patients, only 2 (3%) developed metastases on CT scan during follow-up.
- ctDNA positivity preceded radiographic recurrence by a median of 43 days



Oncological outcome- Immunotherapy at the time of molecular relapse

- In the ctDNA negative patients, both recurrence-free and overall survivals were excellent, as demonstrated in the Kaplan-Meier curves below:



With regards to the primary endpoint, 55% of the 44 patients with a ctDNA+ status converted to ctDNA- with no evidence of disease on CT scanning.

Strengths

Personalized Approach: Tailors treatment based on molecular evidence rather than solely on pathological risk factors.

Early Detection: ctDNA positivity precedes radiographic recurrence by a median of 43 days, offering a window for early intervention .

High Specificity: Low false-positive rate among ctDNA-negative patients supports the reliability of the assay.

Limitations

Non-Randomized Design: Lacks a control group, which may introduce selection bias.

Short Follow-Up: Long-term benefits and potential late recurrences remain to be evaluated.

Resource Intensive: Requires access to specialized assays and frequent monitoring, which may not be feasible in all settings.

Future directions

Randomized Controlled Trials: Needed to validate findings and establish ctDNA-guided therapy as a standard of care.

Integration with Other Biomarkers: Combining ctDNA with other molecular markers may enhance predictive accuracy.

Cost-Effectiveness Analyses: Assessing the economic impact of implementing ctDNA-guided strategies in clinical practice.

Thank you