What if I want to preserve my bladder? Current and future bladder sparing strategies in MIBC

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Disclosures

- Research Support
  - Roche/Genentech, Pfizer, Bicycle, J&J Innovative Medicines, Flare Therapeutics
- Consulting/Advisory Role
  - Astellas, Pfizer, MSD, Abbott Laboratories
- Honorarium
  - Astellas, Pfizer

Case History

- 59-year-old male, presents with hematuria for 2 months
  - Urine cytology: high grade urothelial carcinoma
  - Cystoscopy: 2cm bladder mass
  - ECOG 0, Creatinine 0.9 mg/dL
  - Biopsy: MIBC, cT2N0
  - No hydronephrosis, no CIS
- “I do NOT want to lose my bladder”





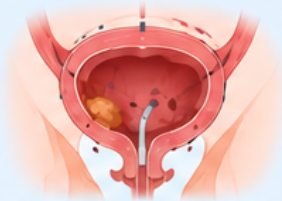
Our patient

- cT2 N0 MIBC
- ECOG 0
- No hydronephrosis
- No CIS

1 Surgery-based approach



Neoadjuvant chemotherapy

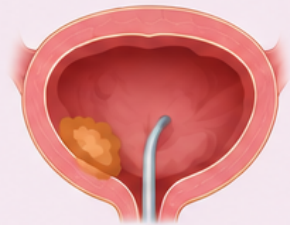


Radical cystectomy

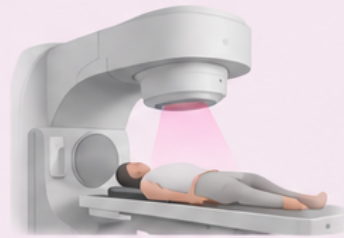


Adjuvant therapy

2 Trimodality Therapy (TMT)



Maximal TURBT



Concurrent chemoradiation

3 True bladder sparing?



Modern systemic therapy



Response-adapted strategy



Radiographic and molecular response assessment

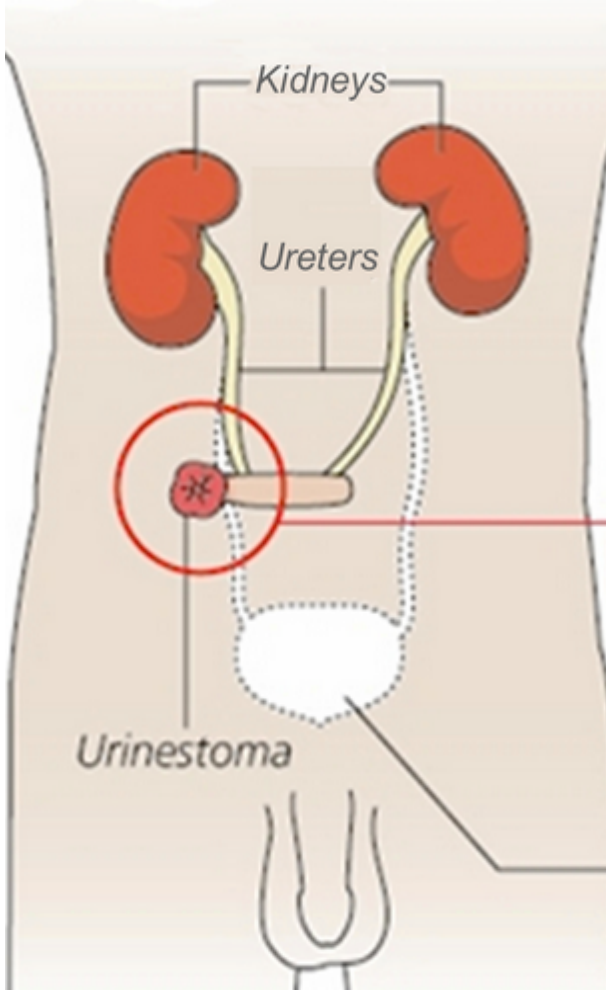
Radical Cystectomy can be curative, but…

Short-term (90 days)

- Any complication 80%
- Major complication 37%
- Readmission 37%
- Mortality 4.7%

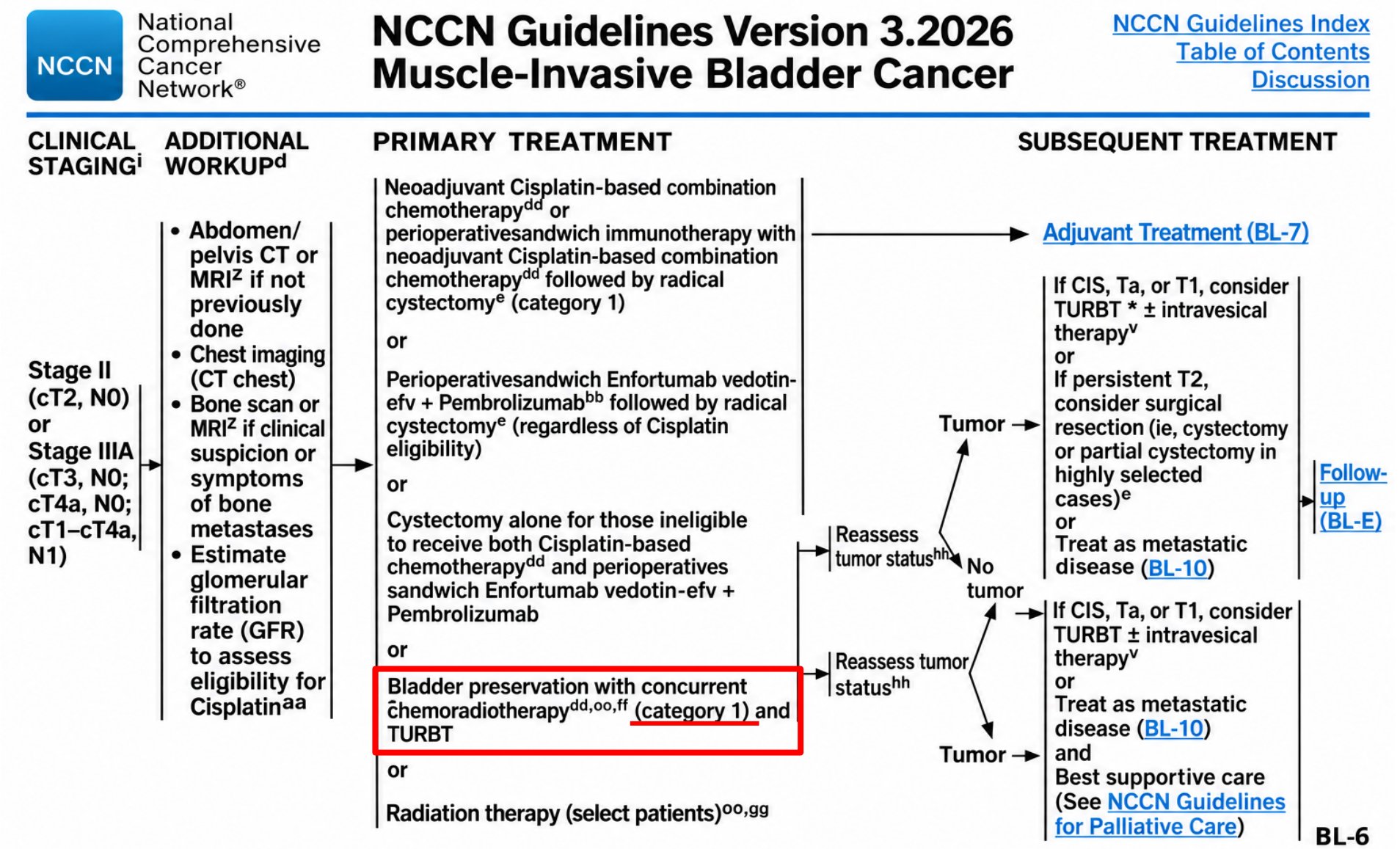
Long-term

- Nighttime incontinence 49%
- Male erectile dysfunction 86%
- Female sexual dysfunction 59%



Maibom et al, Eur Urol Open Sci, 2021; Chappidi et al, Urol Oncol, 2023; Maibom et al, BMJ Open, 2021; Clifford et al, J Urol, 2016; Zahran et al, BJU Int, 2023; Zippe et al, Urology, 2004; Zahran et al, Climacteric, 2016; Yang et al, Surg Oncol, 2016.

TMT is an established standard for selected patients



What are outcomes for TMT?

- Pooled RTOG experience
  - n=486 patients, platinum-containing trials

Outcome	No. of Patients	5 Years			10 Years		
		Estimate (%)	95% CI (%)	No. of Patients at Risk	Estimate (%)	95% CI (%)	No. of Patients at Risk
Local failure, any	212	43	39 to 48	148	48	43 to 53	39
Local failure, muscle invasive	56	13	10 to 17	191	14	10 to 17	52
Local failure, non–muscle invasive	156	31	27 to 36	162	36	32 to 41	44
Nodal recurrence	66	13	10 to 16	199	16	12 to 19	54
Distant metastases	153	31	27 to 36	188	35	30 to 39	53
Disease-specific survival	150	71	67 to 75	205	65	61 to 70	57
Bladder-intact disease-free survival	282	56	51 to 61	173	55	50 to 60	45
Overall survival	262	57	52 to 61	205	36	31 to 42	57

- How does this compare to RC???

Mak et al JCO 2014

www.thelancet.com/oncology Vol 24 June 2023

Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

Alexandre R Zlotta, Leslie K Ballas, Andrzej Niemierko†, Katherine Lajkosz†, Cynthia Kuk, Gus Miranda, Michael Drumm, Andrea Mari, Ethan Thio, Neil E Fleshner, Girish S Kulkarni, Michael A S Jewett, Robert G Bristow, Charles Catton, Alejandro Berlin, Srikala S Sridhar, Anne Schuckman, Adam S Feldman, Matthew Wszolek, Douglas M Dahl, Richard J Lee, Philip J Saylor, M Dror Michaelson, David T Miyamoto, Anthony Zietman, William Shipley, Peter Chung, Siamak Daneshmand, Jason A Efstathiou**

- cT2-T4, N0, n=440 RC, n=282 TMT
- Treated from 2005-2017 at North America academic sites
- Matched for sex, cT2 stage, hydronephrosis, periop chemotherapy

TMT performs well here

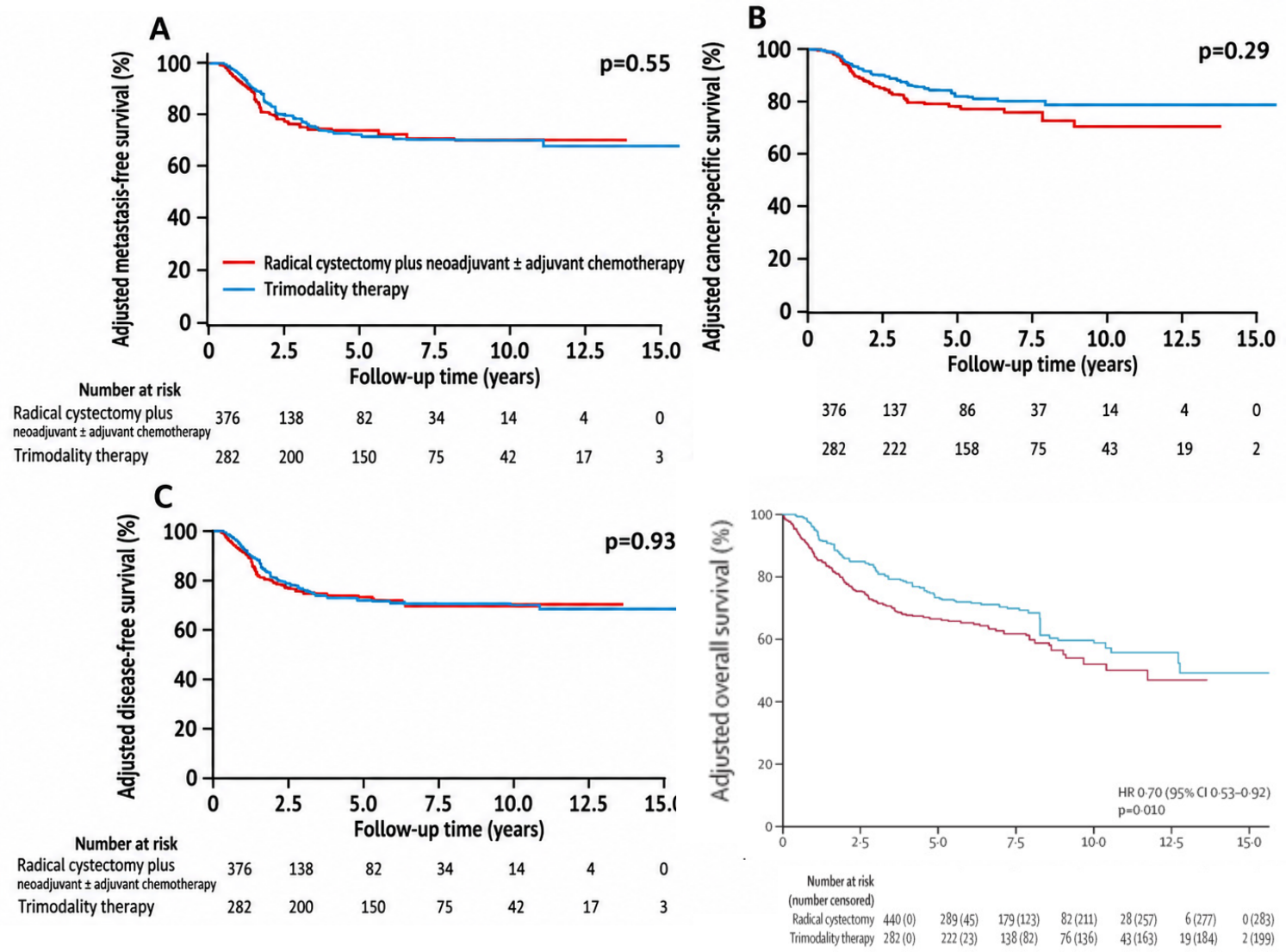
- Modest improvement in **OS** for TMT
  - HR 0·70 [95% CI 0·53–0·92] p=0·010

- No difference in
  - **Metastasis-free survival**

    SHR 0·89 [95% CI 0·67–1·20]

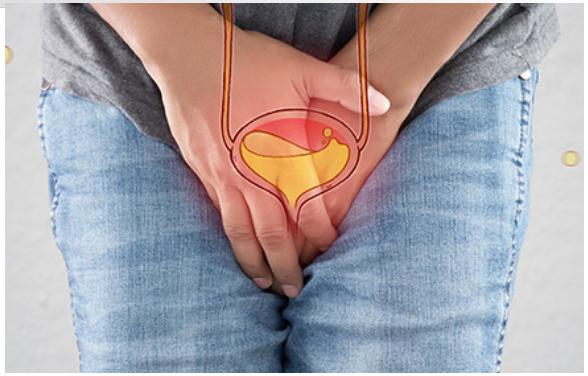
  - **Cancer-specific survival**

    SHR 0.72 [95% CI 0·50–1·04] p=0·071



Zlotta et al Lancet 2023

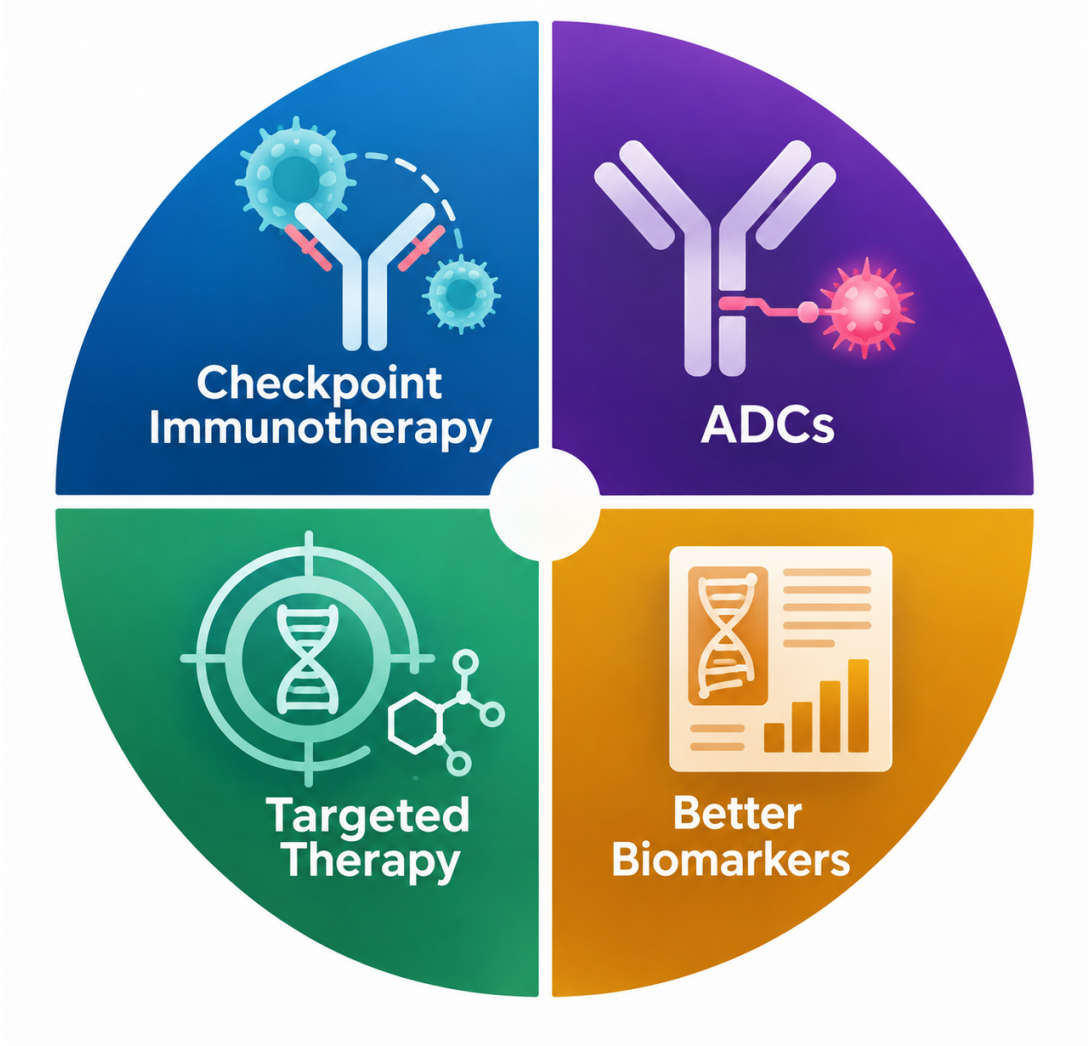
The Challenge with TMT…



Late toxicity	Reported rate (approximate)	Comments
Any late grade 3+ pelvic (GU or GI)	7%	5.7% GU; 1.9% GI
Late grade 4 / treatment-related death	0%	
Diminished bladder capacity / reduced compliance	22–25%	Distressing in ~1/3 of patients
Urinary urgency	15%	
Incontinence / urinary leakage	19%	
Bowel symptoms	22%	Distressing in ~14% of patients
Cystectomy for treatment-related bladder dysfunction	1–2%	Without recurrent cancer
Normal bladder function on long-term urodynamics	75%	

Zeitman et al J Urol 2003

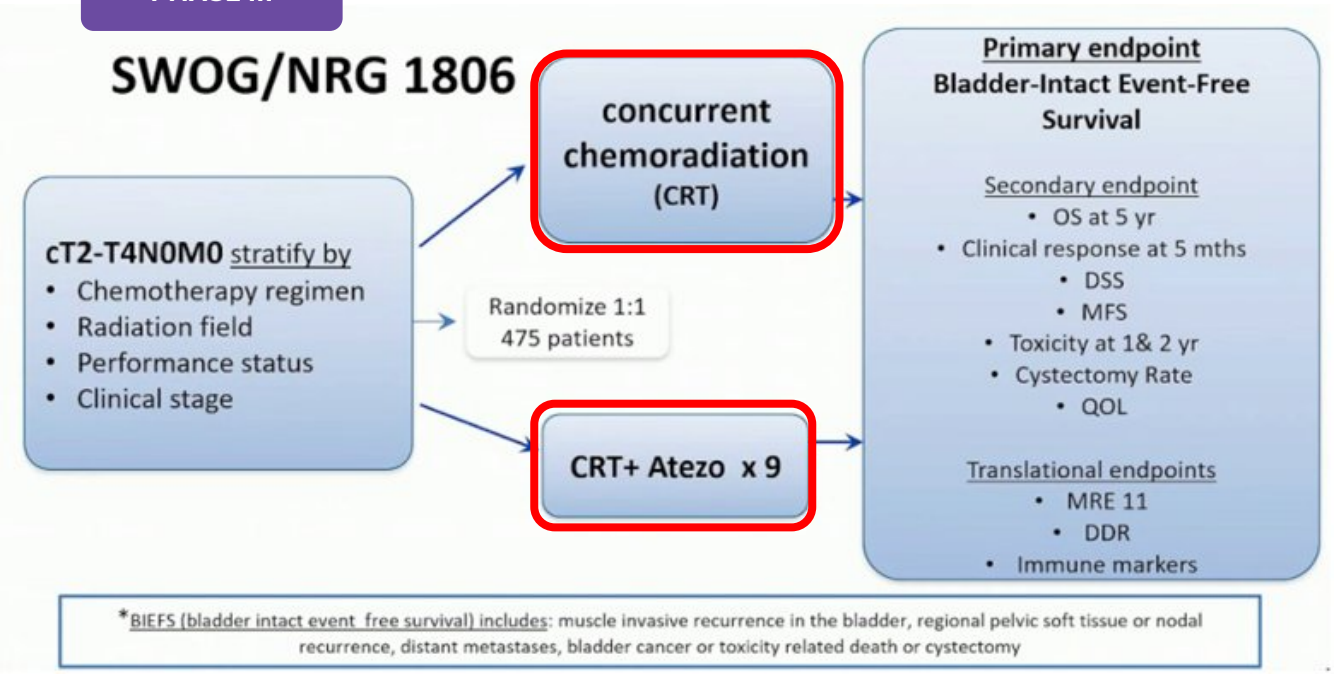
But we are in a new era!



How can we best use these tools to preserve the bladder???

Novel approaches to Radiation: Phase III trials

PHASE III



PHASE III

ARCHER (NRG-GU015)

Hypofractionated RT
55 Gy / 20 fractions

versus

Ultra-hypofractionated RT
32.5 Gy / 5 fractions

Both with radiosensitizing chemotherapy

Can we make bladder-preserving RT much shorter?

Singh et al BCAN 2025

EV + Pembro + RT: A UCSF Approach

EV-PRIME

UCSF Investigator-Initiated
NCT06470282

PHASE IB/II • N=47

PATIENT COHORT
Ineligible / declining surgery
(cT2-4a, N0-1)

KEY ENDPOINTS
6-Month cCR rate (Primary)
RFS, OS

CONCURRENT (6 WKS)

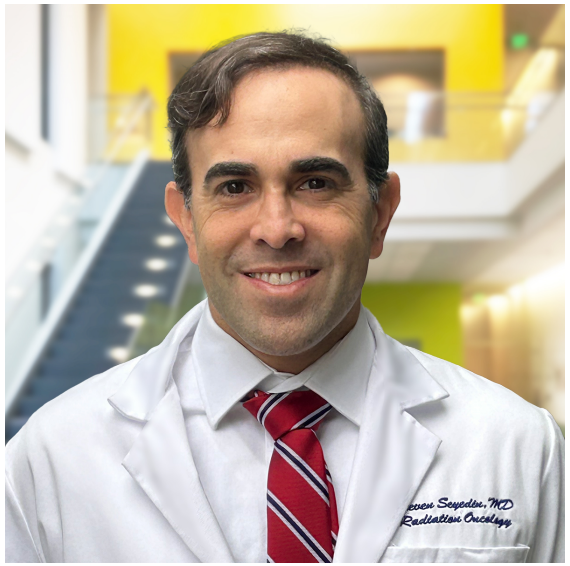
Radiotherapy (64Gy / 32Fx)
+ EV & Pembrolizumab (2 Cycles)

ADJUVANT (CONSOLIDATION)

Adjuvant EV (3 additional cycles)
+ Pembrolizumab (15 additional cycles)



Vadim Koshkin, MD



Steven Seyedin, MD



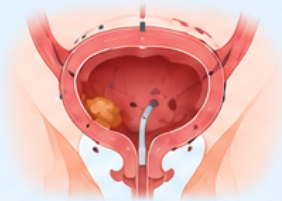
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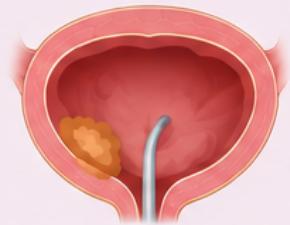


Radical cystectomy

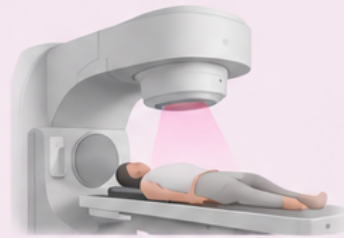


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3 True bladder sparing?



Modern systemic therapy



Response-adapted strategy



Radiographic and molecular response assessment



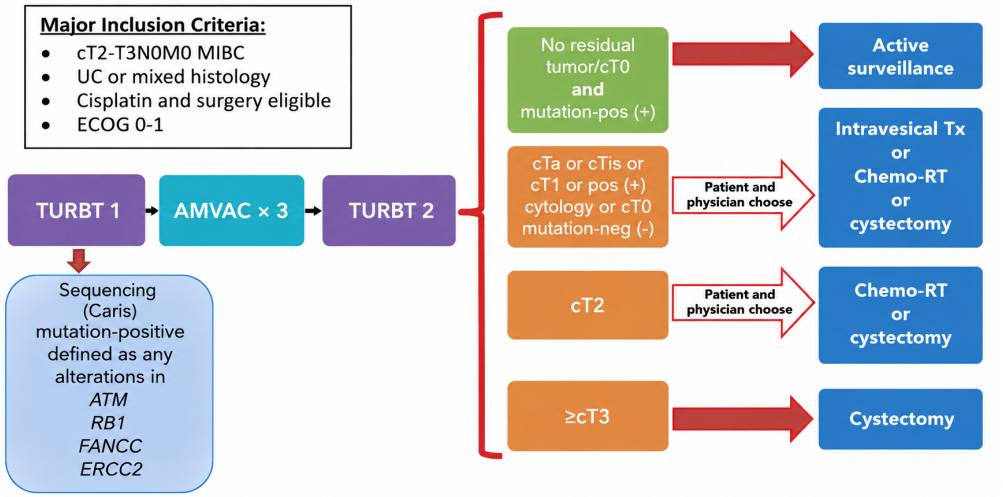
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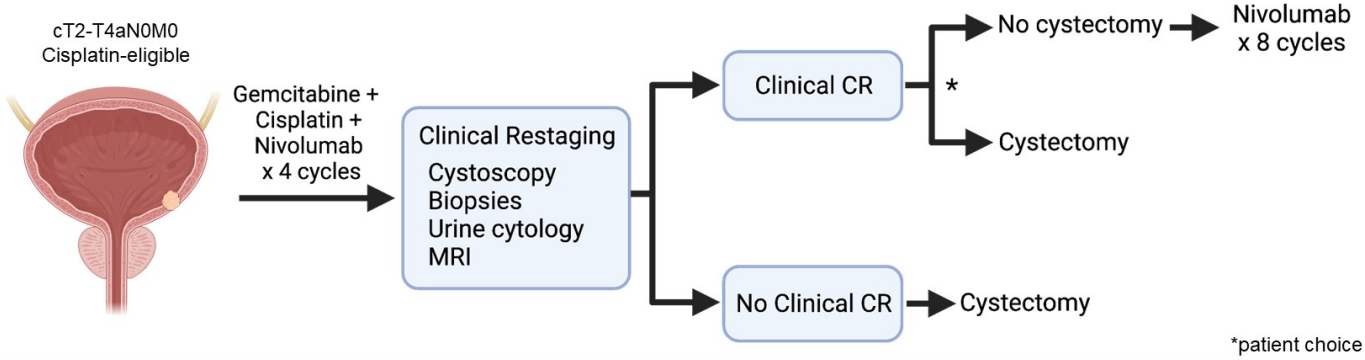
3 True bladder sparing?



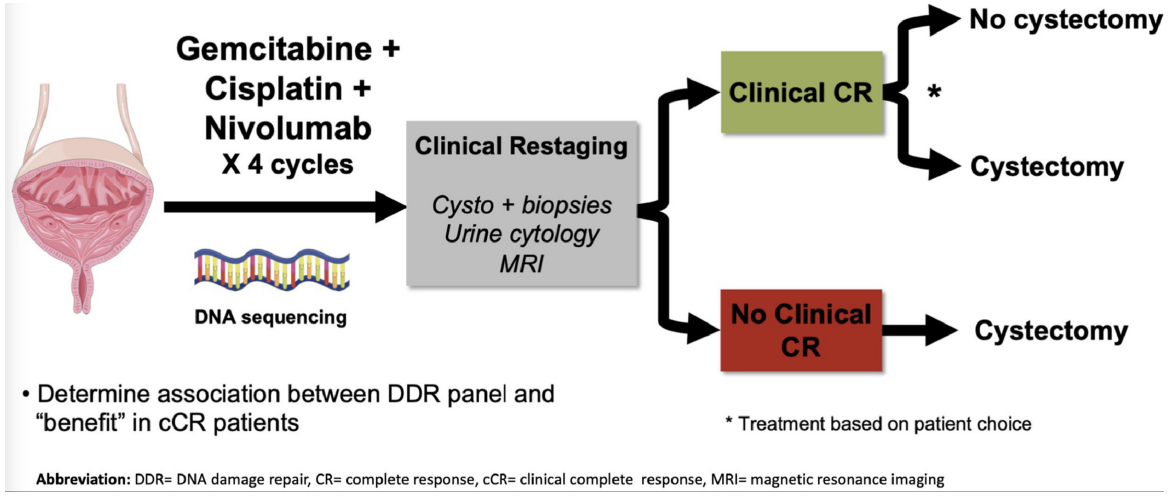
RETAIN-1



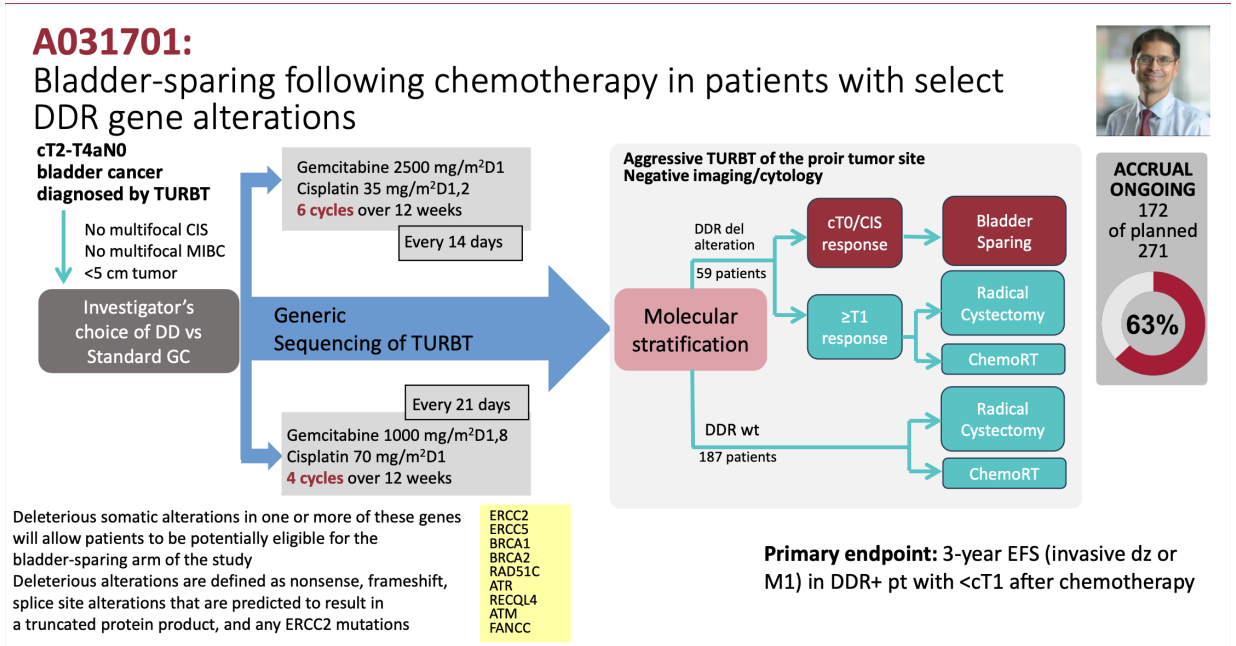
HCRN GU 16-257



RETAIN-2

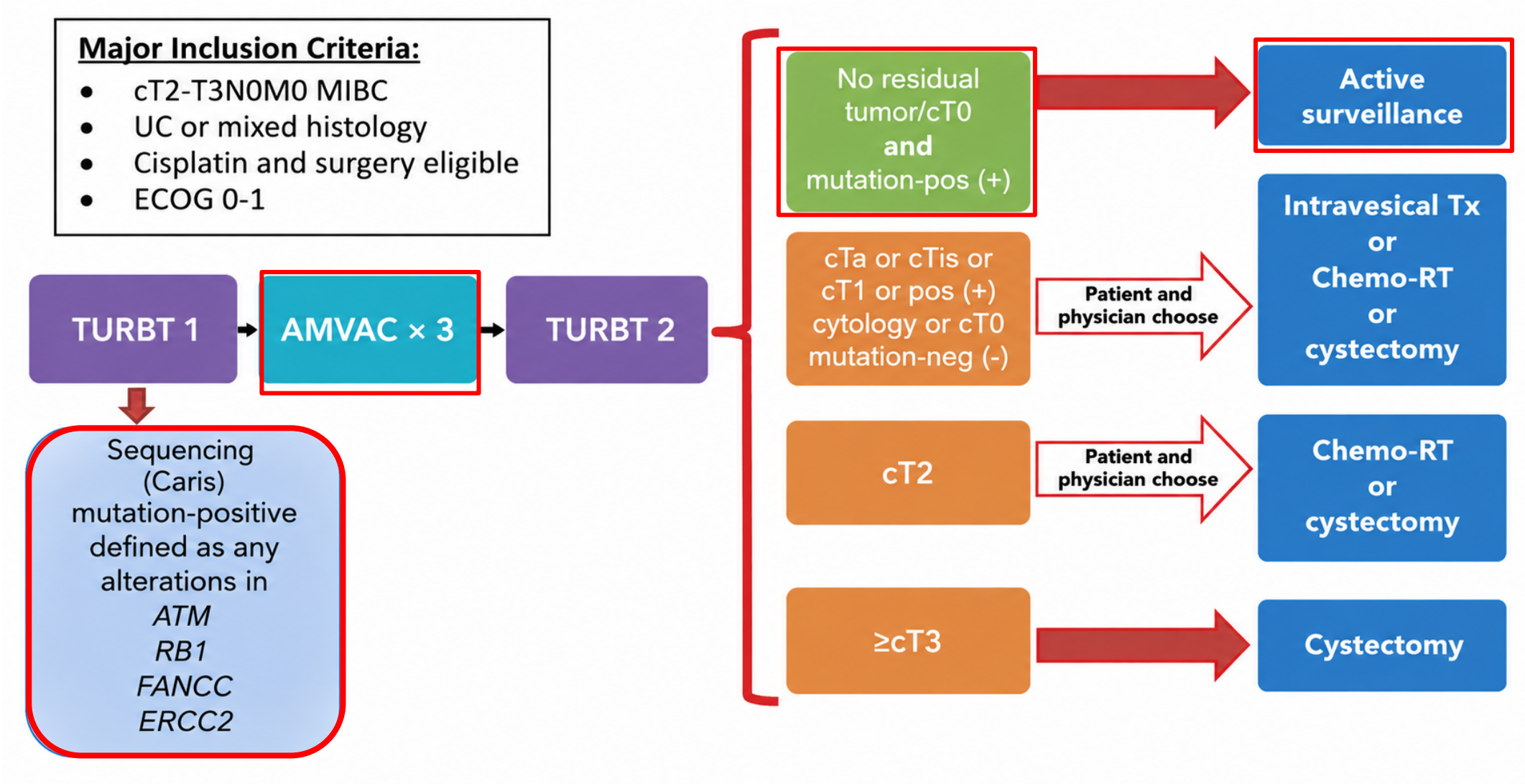


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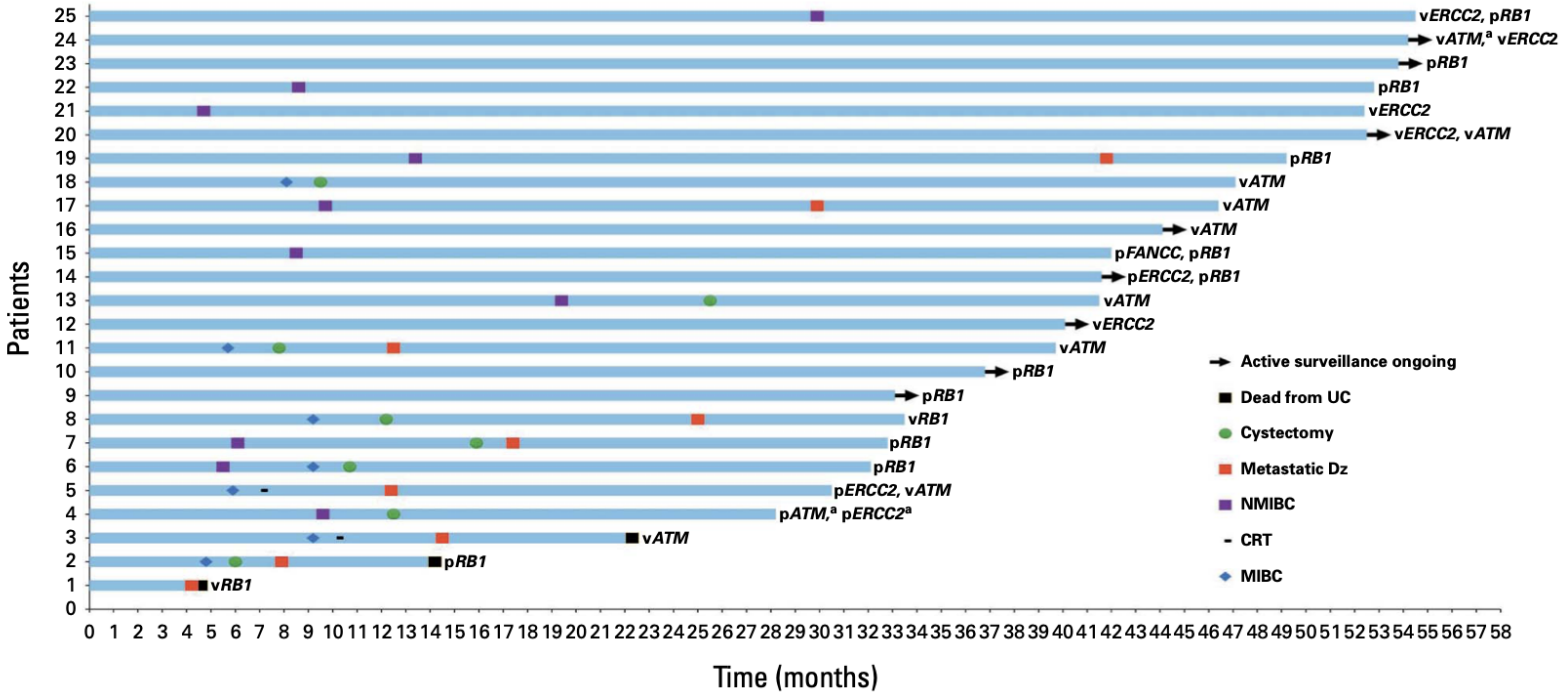
Geynisman et al, J Clin Oncol, 2025; Ghatalia et al, J Clin Oncol, 2025; Galsky et al, Nat Med, 2023; Iyer et al, J Clin Oncol, 2022.

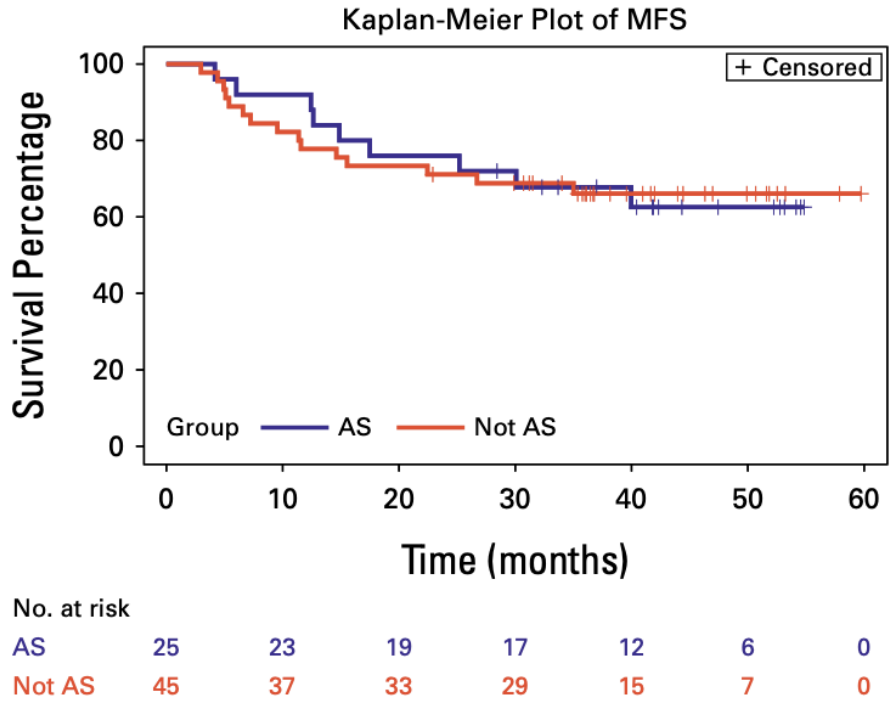
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Geynisman et al, J Clin Oncol, 2025

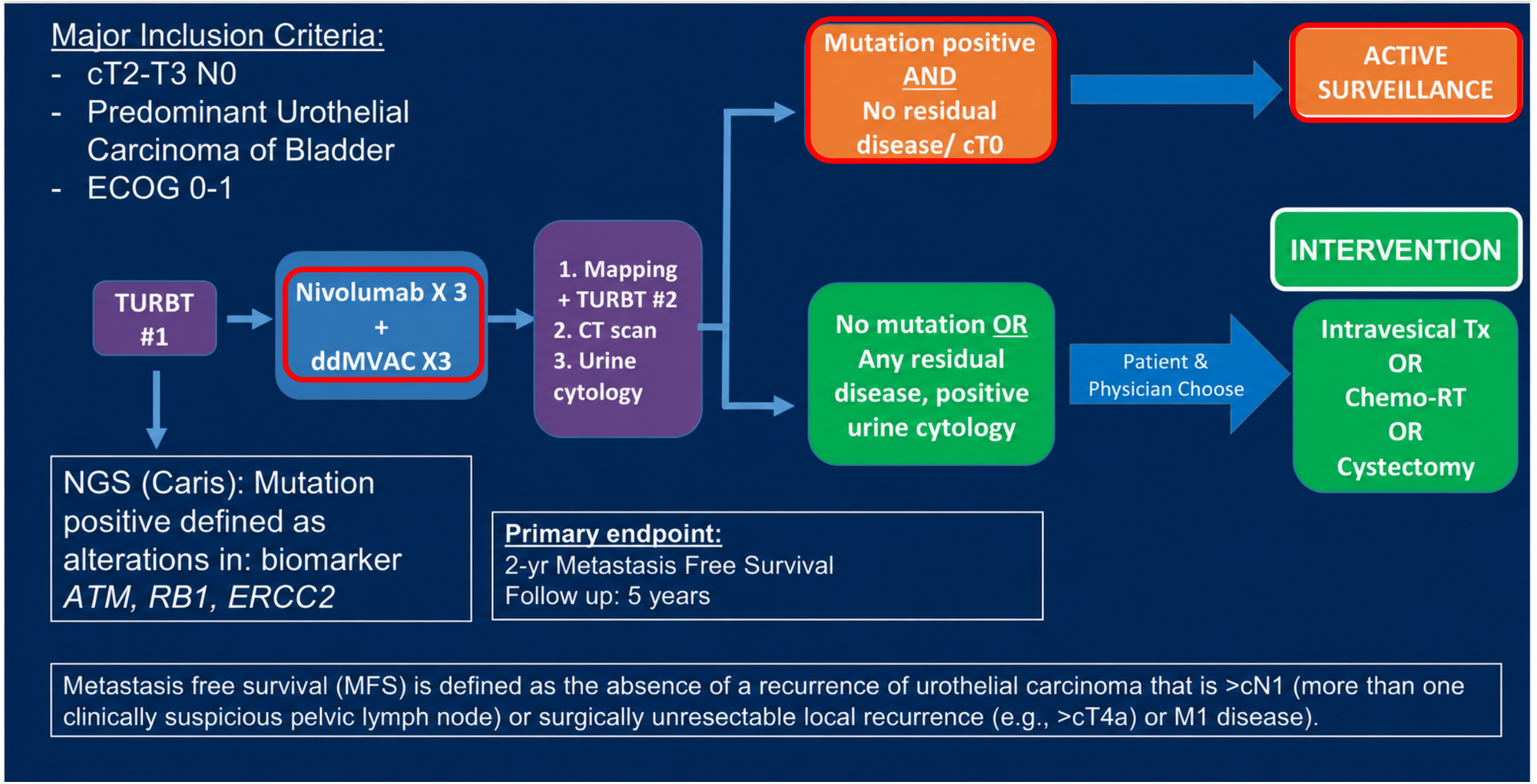
RETAIN-1: Room for Improvement



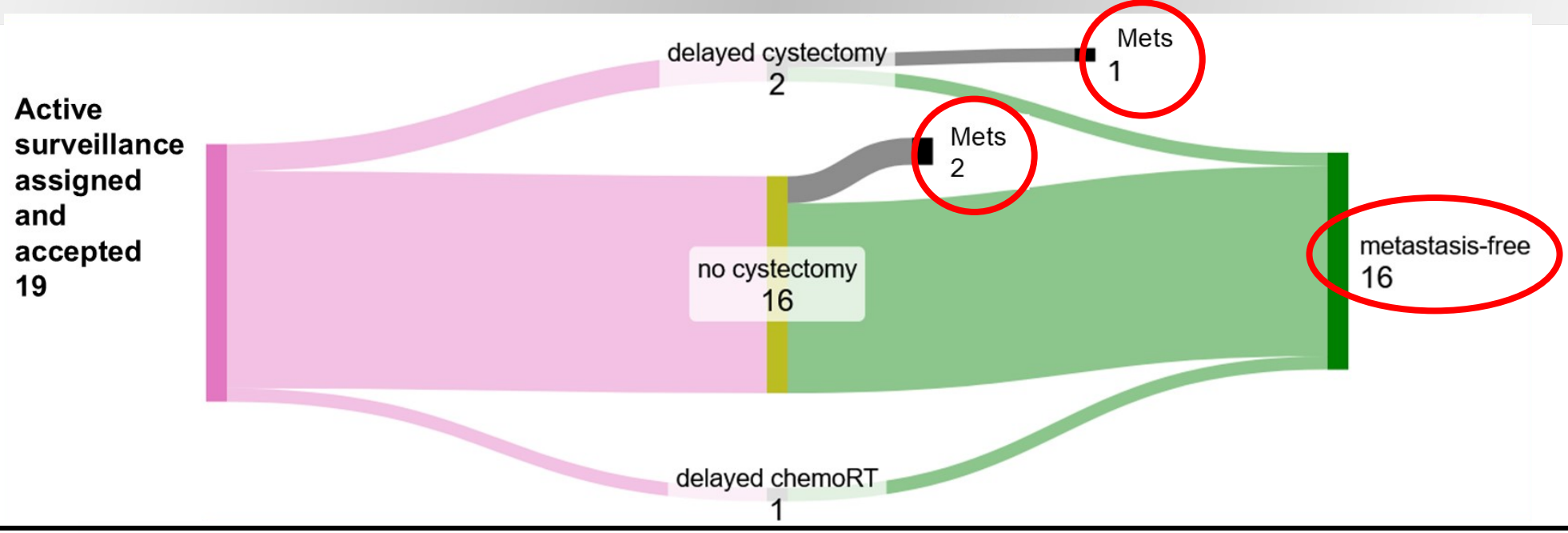


Parameter	Result
Recurrence in AS cohort	17/25 (68%)
Metastatic disease in AS cohort	9/25 (36%)
MFS + intact, un-radiated bladder (AS)	12/25 (48%)

RETAIN-2 – will PD-1 immunotherapy help?



Ghatalia et al, GU ASCO, 2025





Ghatalia et al, GU ASCO, 2025

RETAIN-2 –better outcomes

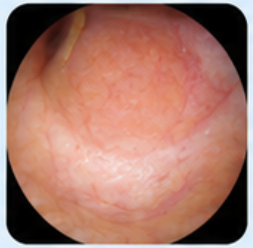
	RETAIN-1 (ddMVAC)	RETAIN-2 (ddMVAC + nivolumab)
In AS – metastases-free	64%	82%
In AS – no local recurrence	38%	68%
In AS – metastases-free with intact unradiated bladder	48%	60%

Ghatalia et al, GU ASCO, 2025

The Elephant in the Room: Clinical Restaging in MIBC is NOT precise

Current modalities can miss residual ≥ pT2 disease and overestimate complete response

Cystoscopy



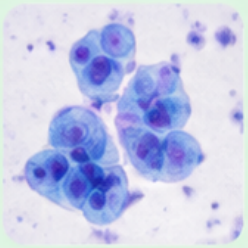
- Visual assessment of bladder mucosa
- Identifies visible tumor and obstructive lesions

TURBT / Biopsy



- Targeted or systematic biopsies
- Provides histologic confirmation and local staging

Urine Cytology



- High specificity for high-grade disease
- Non-invasive assessment of urothelial cells

CT / MRI



- Assesses bladder wall, perivesical fat, nodes, and distant disease
- Used for clinical T and N staging

False downstaging

32% – 35.7%

of patients with residual ≥pT2 disease are understaged by clinical restaging.[1-3]

Up to

60%

of patients are misclassified as cT0 after cystoscopy.[4]

Systematic cystoscopy/biopsies can miss nearly

30%

of ≥pT2 disease.[5]

cCR does not reliably predict pCR

1. Li K, et al. *J Clin Oncol*. 2026. ASCO Educational Book. Bladder Preservation in Muscle-Invasive Bladder Cancer.
2. Herr HW. *J Urol*. 2001;166:1286-1291.
3. van Rhijn BWG, et al. *Eur Urol*. 2010;58:146-153.
4. Solsona E, et al. *J Urol*. 2000;164:1688-1692.
5. Grimm MO, et al. *Eur Urol*. 2013;64:993-999.

Can MRI Inform the Decision?

EUROPEAN UROLOGY 77 (2020) 636–643

Urothelial Cancer

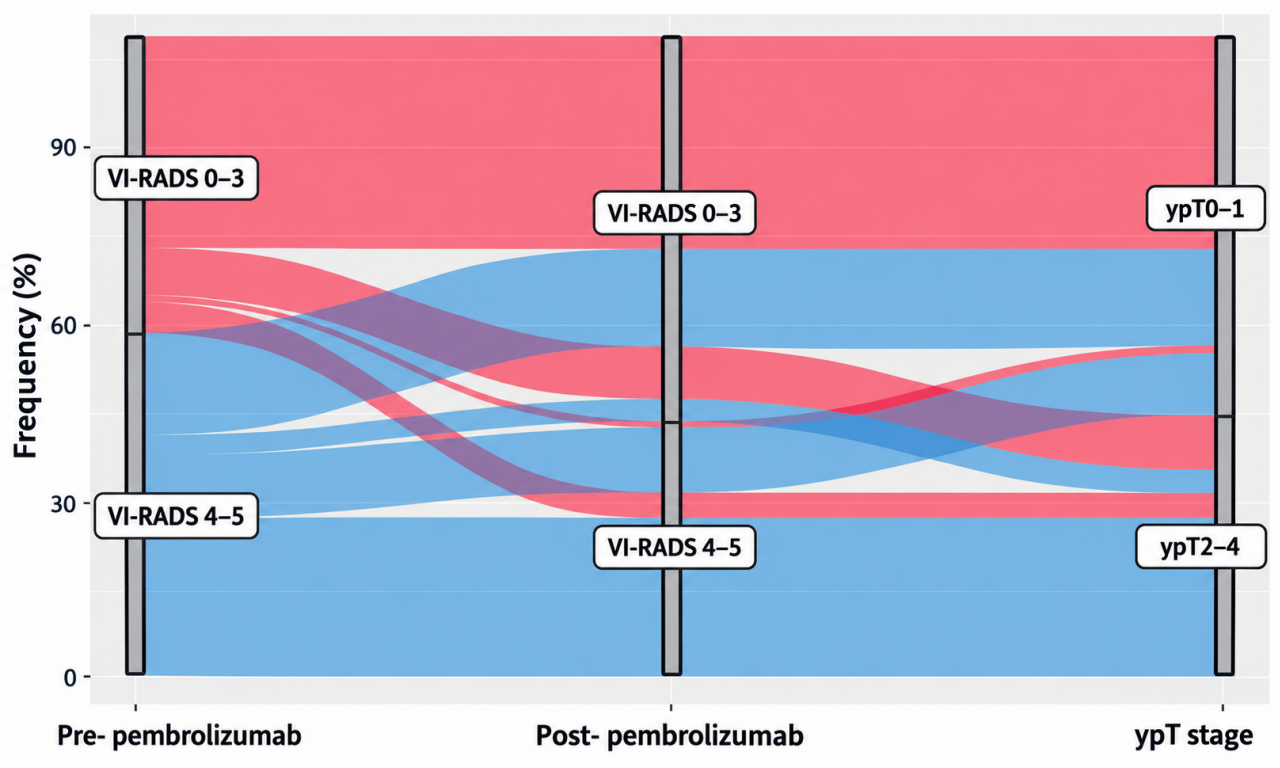
Multiparametric Magnetic Resonance Imaging as a Noninvasive Assessment of Tumor Response to Neoadjuvant Pembrolizumab in Muscle-invasive Bladder Cancer: Preliminary Findings from the PURE-01 Study

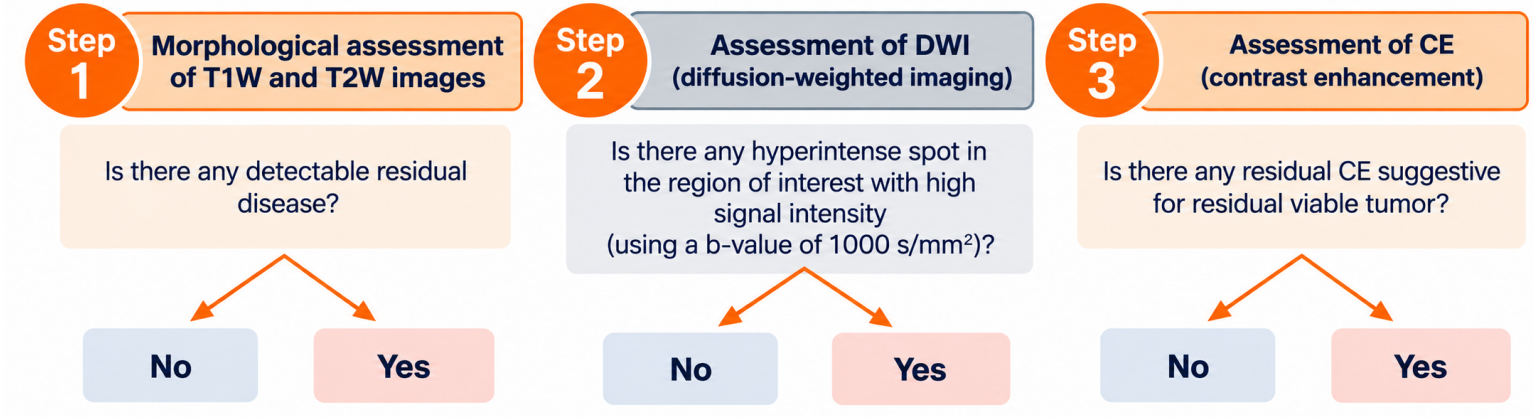
Andrea Necchi[a,*], *Marco Bandini*[b,†], *Giuseppina Calareso*[a,†], *Daniele Raggi*[a], *Filippo Pederzoli*[b], *Elena Farè*[a], *Maurizio Colecchia*[a], *Laura Marandino*[a], *Marco Bianchi*[b], *Andrea Gallina*[b], *Renzo Colombo*[b], *Nicola Fossati*[b], *Giorgio Gandaglia*[b], *Umberto Capitanio*[b], *Federico Dehò*[b], *Patrizia Giannatempo*[a], *Roberta Lucianò*[b], *Andrea Salonia*[b], *Russell Madison*[c], *Siraj M. Ali*[c], *Jon H. Chung*[c], *Jeffrey S. Ross*[c,d], *Alberto Briganti*[b,e], *Francesco Montorsi*[b,e], *Francesco De Cobelli*[e,f,‡], *Antonella Messina*[a,‡]

[a] *Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy;* [b] *Unit of Urology, Division of Experimental Oncology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Milan, Italy;* [c] *Foundation Medicine Inc., Cambridge, MA, USA;* [d] *Upstate Medical University, Syracuse, NY, USA;* [e] *Vita-Salute San Raffaele University, Milan, Italy;* [f] *Clinical and Experimental Radiology Unit, IRCCS San Raffaele Hospital, Milano, Italy*

Can MRI Inform the Decision?

- Somewhat
- 73% (n=19) of predicted cT0 = pT0
- 96% (n=25) of predicted cT0 = pT1 or less
- Neg Predictive Value 62–73%





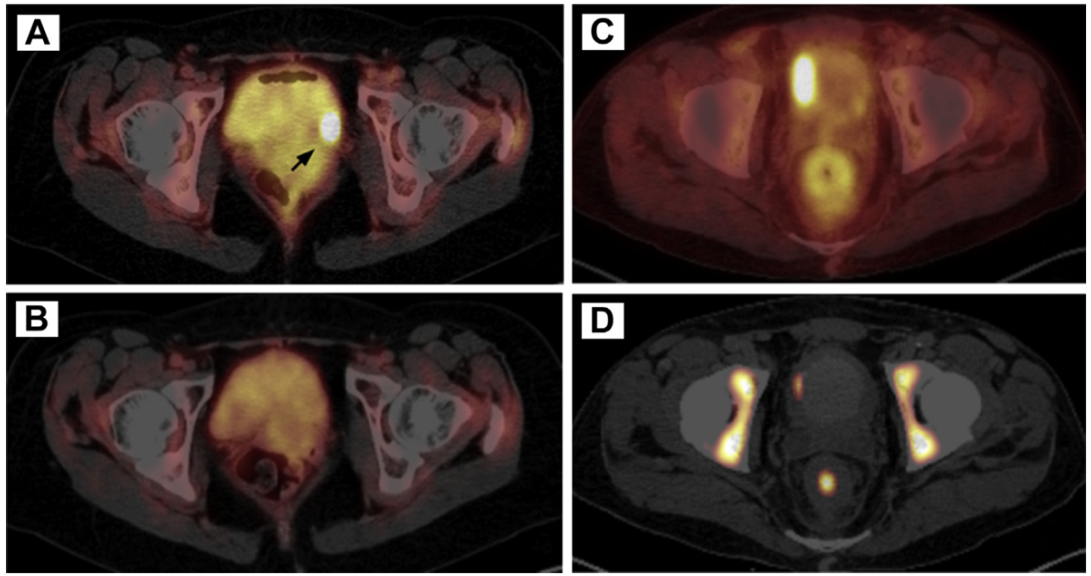
Necchi et al Eur Urol 2020; and BJUI 2024

What about FDG PET?

- Limited by tracer accumulation in the bladder
- Sensitivity only 75% for pCR detection

Pre NAC

Post NAC



Original Study

Check for updates

FDG-PET/CT for Assessing the Response to Neoadjuvant Chemotherapy in Bladder Cancer Patients

Ayman Soubra,[1] Mehmet Gencturk,[2] Jerry Froelich,[2] Priya Balaji,[1] Shilpa Gupta,[3] Gautam Jha,[3] Badrinath R. Konety[1]

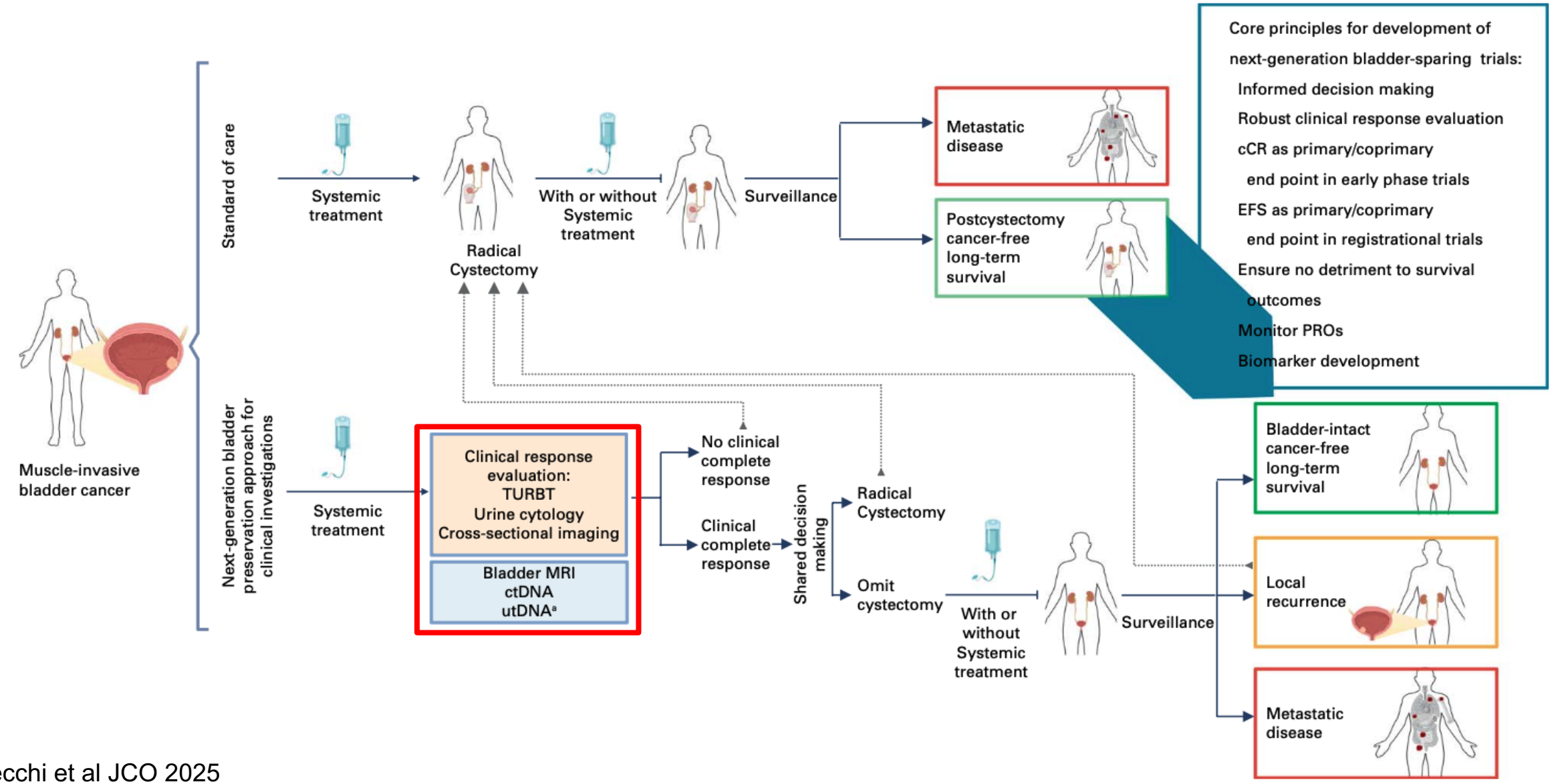
Clinical Genitourinary Cancer, Vol. 16, No. 5, 360-4 © 2018 Elsevier Inc. All rights reserved.
Keywords: Clinical response, Pathologic stage, Urinary bladder neoplasms, Urothelial carcinoma

Table 2 Accuracy of FDG-PET/CT in Detecting Complete Response

SUV_{max} Reduction	No Tumor on Pathology	Residual Tumor on Pathology
100%	6	3
< 100% or no change	2	26
Characteristic	**Value**	**95% CI**
Sensitivity	75%	34.9-96.81
Specificity	89.66%	72.65-97.81
Positive LR	7.25	2.31-22.75
Negative LR	0.28	0.08-0.93

Abbreviations: CI = confidence interval; FDG-PET/CT = ^{18}F-fluorodeoxyglucose with positron emission tomography and computed tomography; LR = likelihood ratio; SUV_{max} = standardized maximum uptake value.

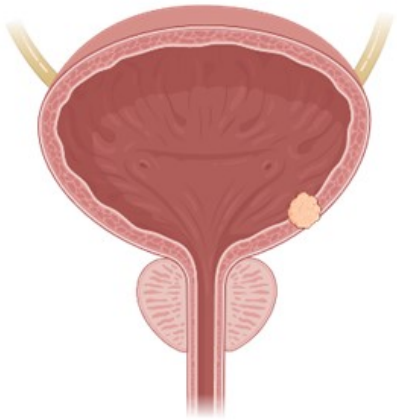
Consensus cCR Endpoints for Bladder Preservation



Necchi et al JCO 2025

HCRN GU 16-257
Improving Patient Selection for Bladder Preservation

cT2-T4aN0M0
Cisplatin-eligible



Gemcitabine +
Cisplatin +
Nivolumab
x 4 cycles

Clinical Restaging
Cystoscopy
Biopsies
Urine cytology
MRI

- Clinical CR
  - No cystectomy → Nivolumab x 8 cycles
  - *
  - Cystectomy
- No Clinical CR → Cystectomy

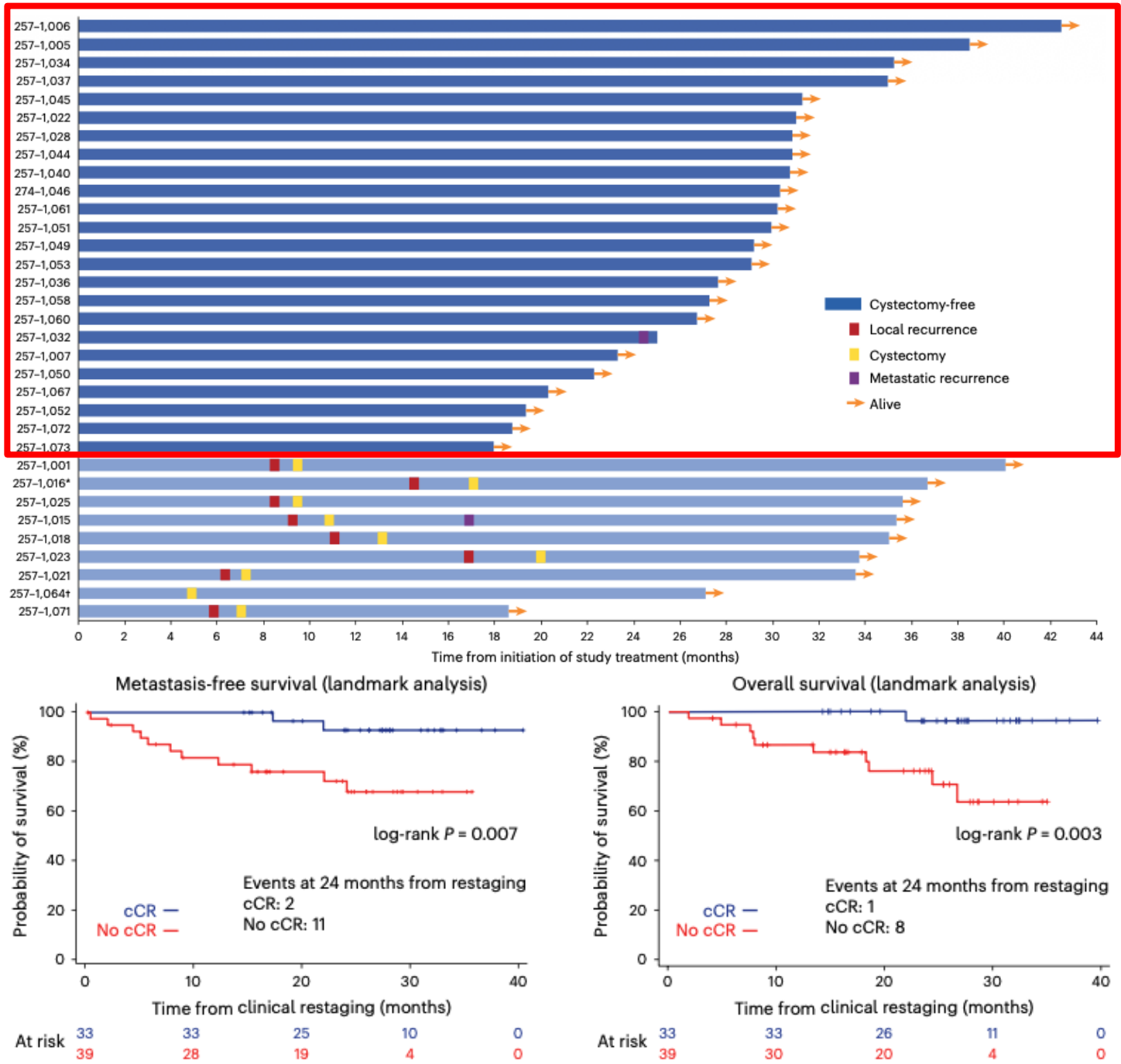
*patient choice

Galsky et al Nat Med 2023

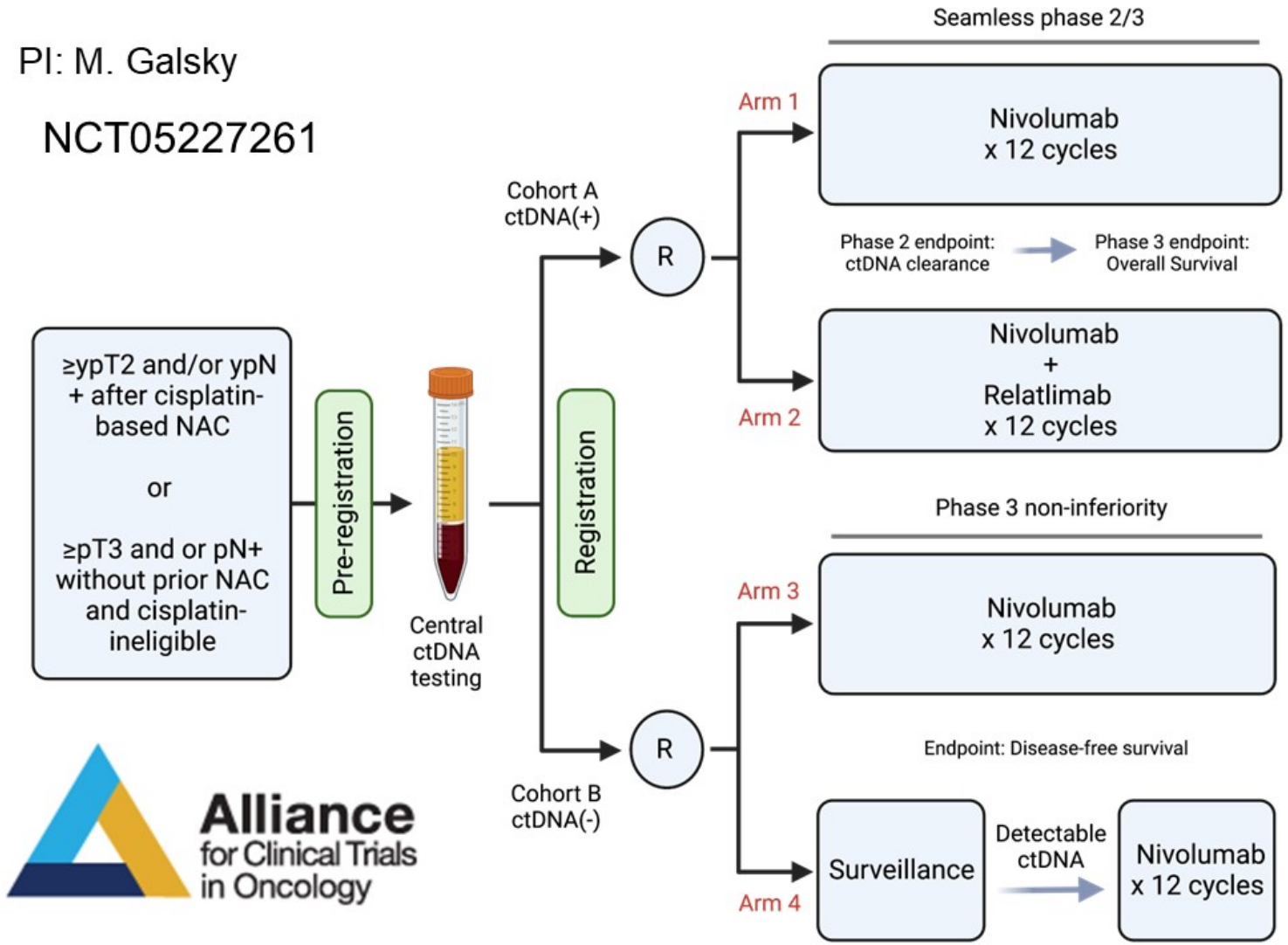
GU16-257

Preservation within reach?

- 76% deferring cystectomy without recurrence
- More stringent cCR defition performed much better
  - PPV for composite endpoint: 0.97 (95% CI: 0.91, 1)
- DDR mutations did **not** improve selection

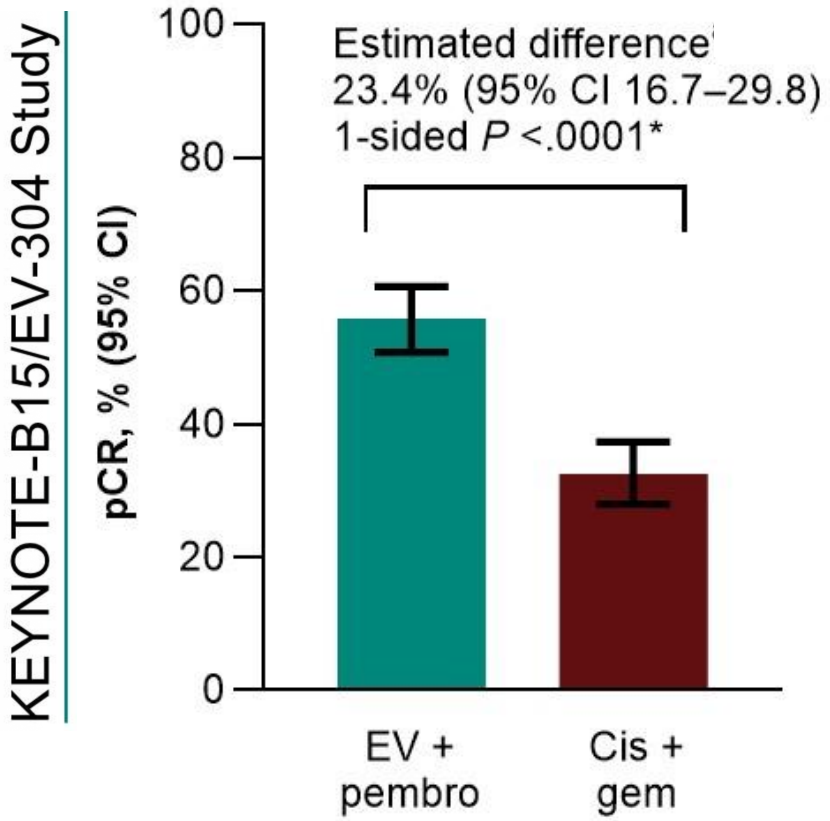


In Progress: The MODERN A032103 Trial



Galsky et al ASCO 2024

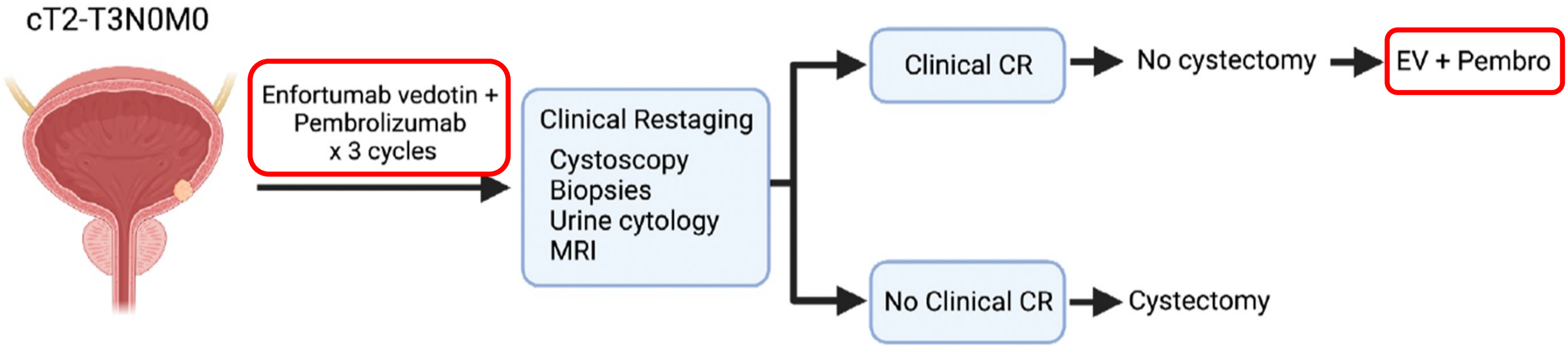
EV + Pembrolizumab is Changing the Story



Can Surgery Be Avoided?

Galsky et al GU ASCO 2026

HCRN GU22-598: Phase 2 trial of enfortumab vedotin plus pembrolizumab with selective bladder sparing for treatment of muscle-invasive urothelial cancer of the bladder



https://hoosiercancer.org/all-clinical-trials/hcrn-gu22-598/

EV-209 | Bladder preservation with EV + pembrolizumab

Phase 2 • single-arm • estimated n=240 • recruiting

MIBC
Candidates for cystectomy
Electing bladder preservation

cT2–T4aN0M0 or T1–T4aN1M0
Predominant urothelial histology
≥50%
ECOG 0–2

→ **EV + Pembrolizumab Days 1 & 8 / Day 1 q3 weeks**

Cycles 1–4

→ **Response assessment Cystoscopy/TURBT Urine cytology + imaging**

→ **Continue EV + pembrolizumab through cycle 9 if responding / tolerable**

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Predominant urothelial histology ≥50%
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→ **EV + Pembrolizumab Days 1 & 8 / Day 1 q3 weeks**

Cycles 1–4

→ **Response assessment**
Cystoscopy/TURBT
Urine cytology + imaging

→ **Continue EV + pembrolizumab through cycle 9 if responding / tolerable**

EV-309 | EV + pembrolizumab vs concurrent chemoradiotherapy

Phase 3 • randomized • estimated n=390 • recruiting

MIBC
Electing bladder preservation (or ineligible for cystectomy)

cT2–T4aN0M0
Predominant urothelial histology
Fit for systemic therapy
ECOG 0–2

→ **1:1 Randomization**

Arm A

→ **EV + Pembrolizumab**
EV Days 1 & 8
q3 weeks × 9 cycles

→ **Bladder-intact surveillance**

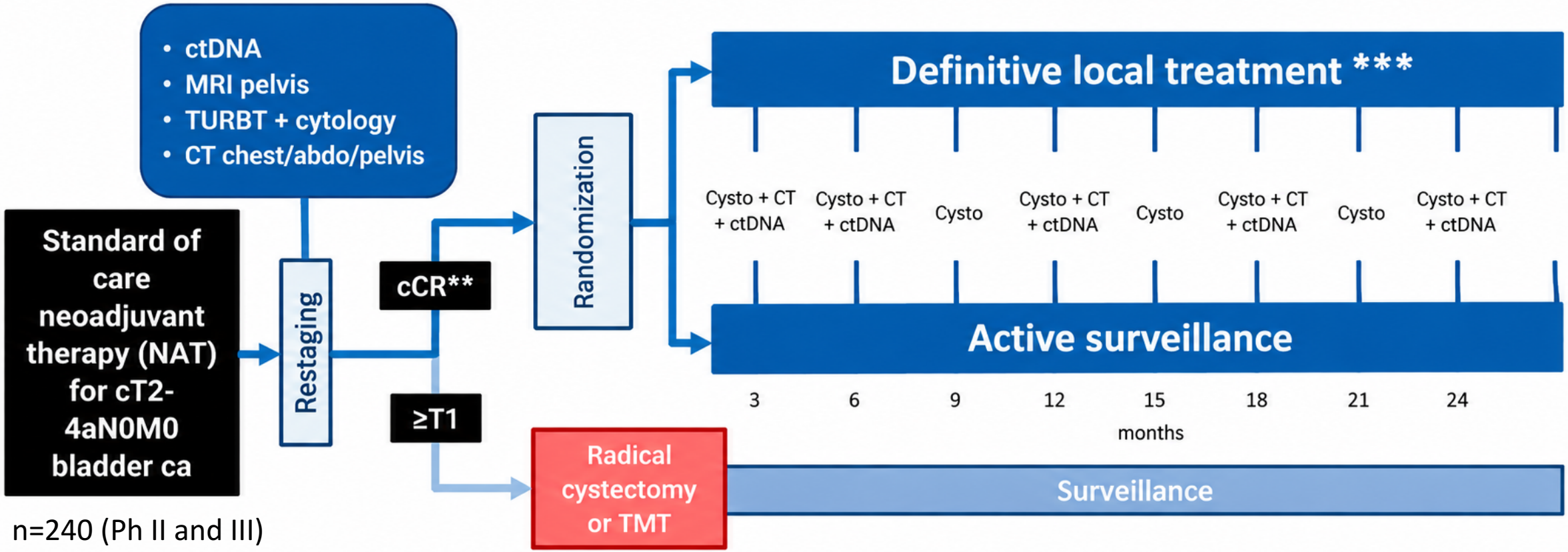
ARM B

→ **Concurrent chemoradiotherapy**
64 Gy / 32 fx OR 55 Gy / 20 fx
+ protocol radiosensitizer

→ **Bladder-intact surveillance**

NEO-BLAST: Neoadjuvant Therapy for Bladder Cancer Followed by Active Surveillance vs Treatment

NCT06537154

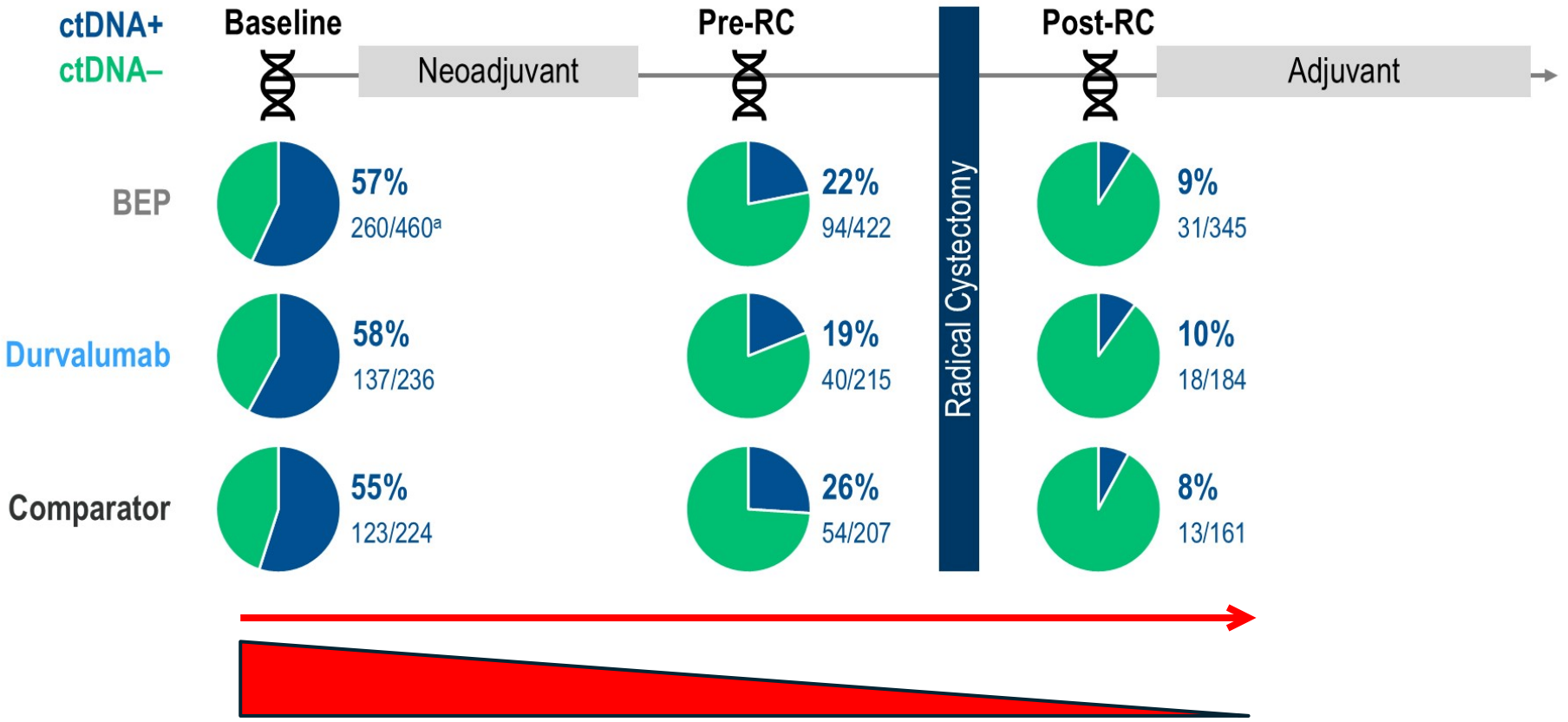


n=240 (Ph II and III)

St-Laurent et al, J Clin Oncol, 2025 (TPS890)

How Can ctDNA Inform this Decision?

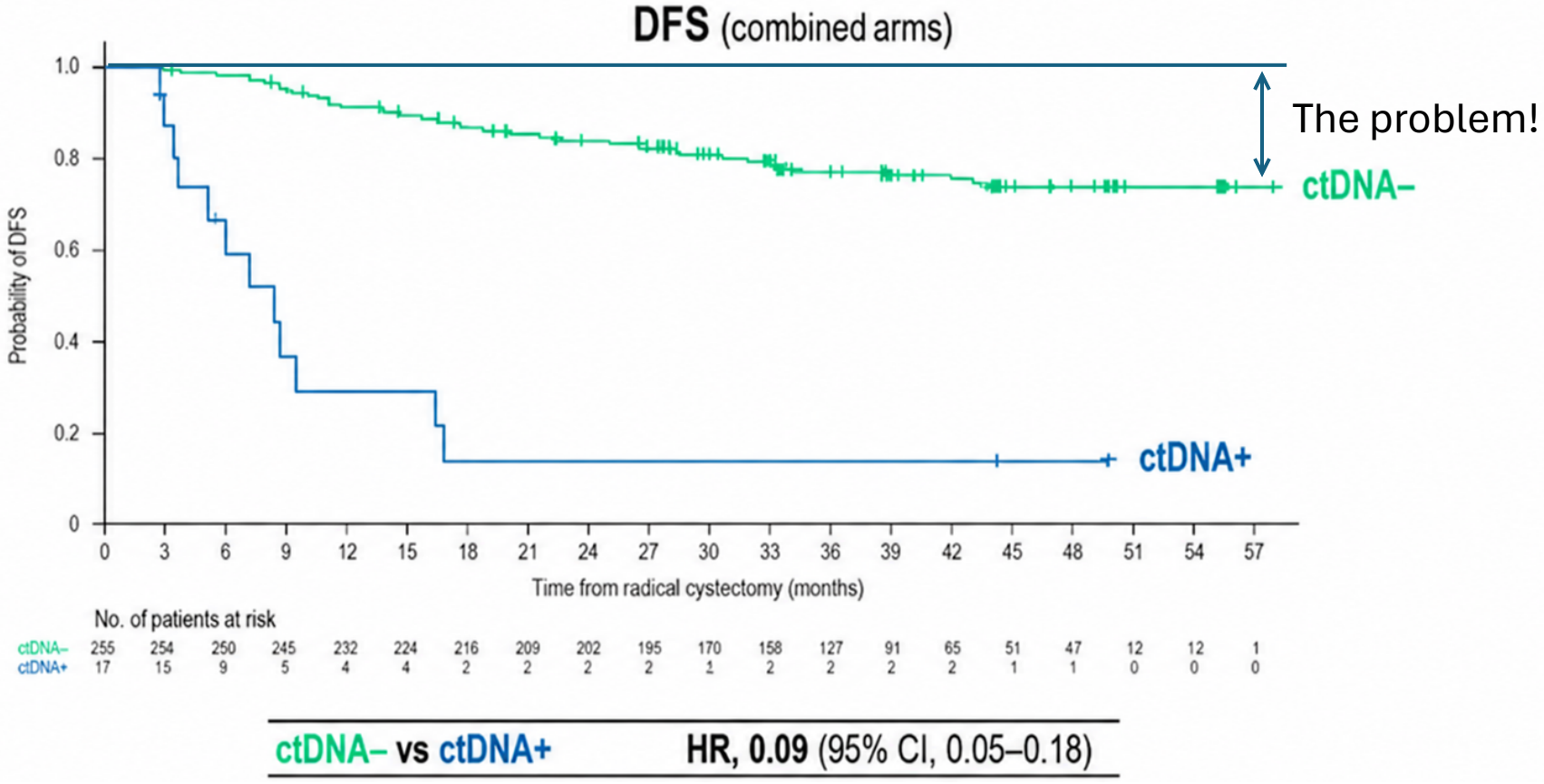
NIAGARA Trial –ctDNA detection decreases with Rx



Powles *et al. ASCO* 2025

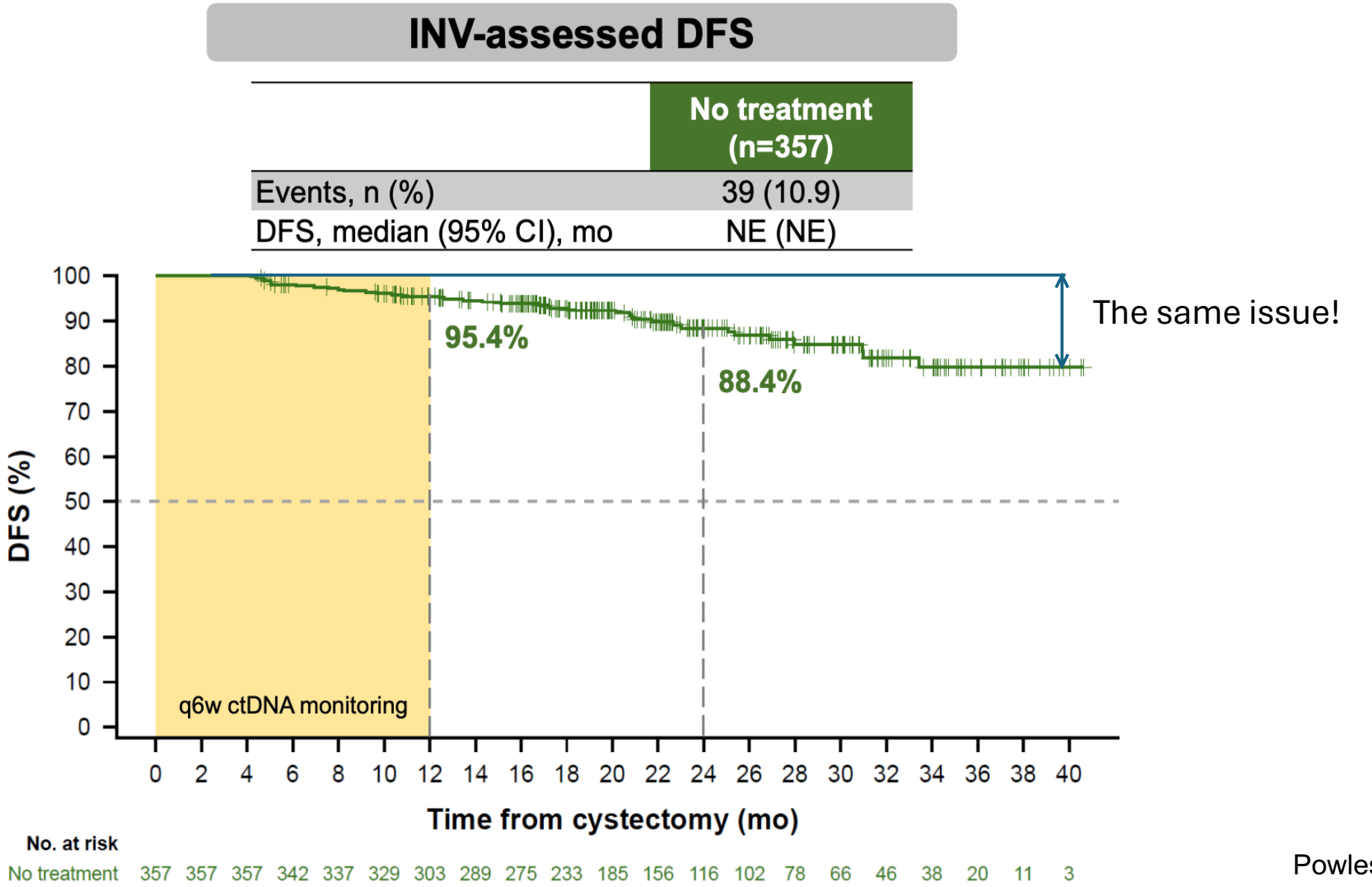
What can ctDNA tell us about long term outcomes?

NIAGARA Trial



Powles *et al. ASCO* 2025

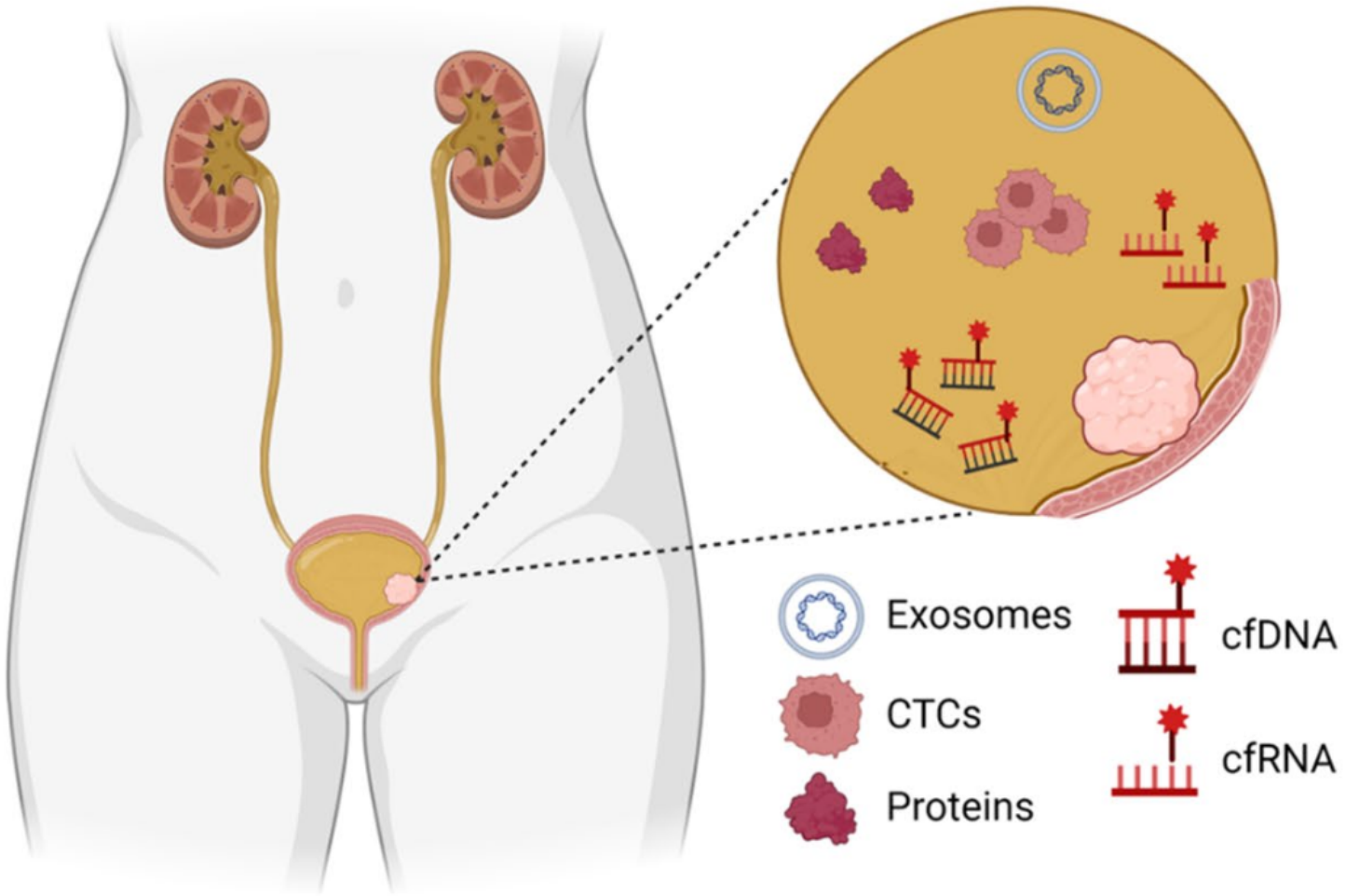
Similar Challenge in IMvigor 011



The same issue!

Powles *et al. ESMO* 2026

Can utDNA inform the discussion?



Limitations

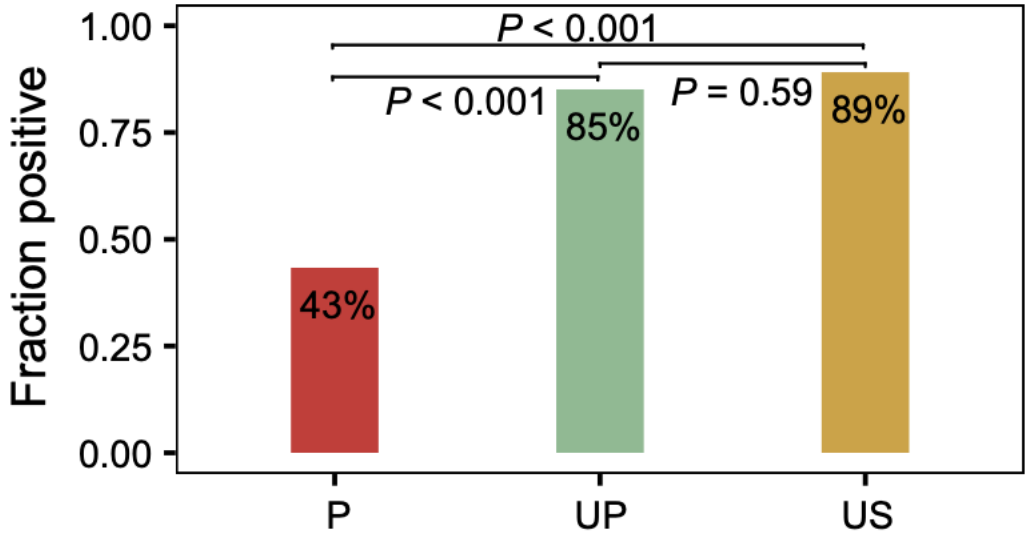
Tumor-informed vs uninformed

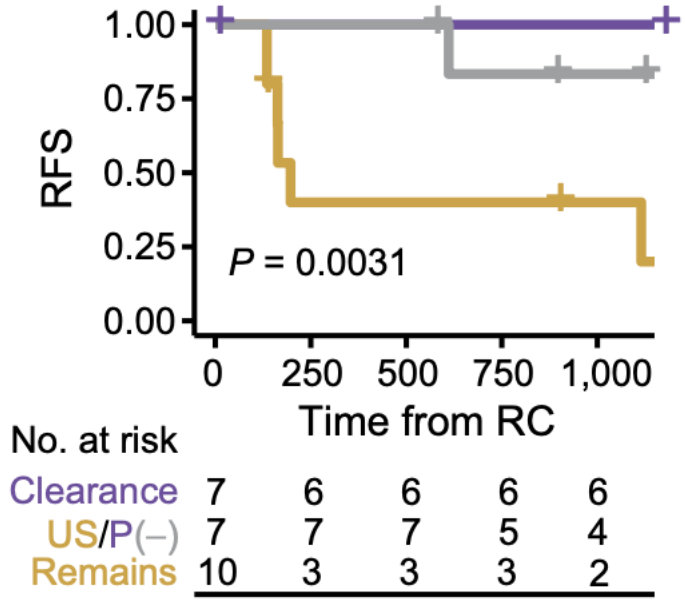
No standardized assay

Linscott *et al. Curr Onc Rep* 2026

utDNA may be more sensitive than ctDNA

- n=92 treated with NAC and RC
- DNA more commonly detected in urine supernatant (89%) than plasma (43%)
- Combined utDNA and ctDNA assessment strongly prognostic for relapse





Christensen *et al. Clin Can Res* 2023

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES

Monitoring of plasma and urine tumor-derived DNA to inform bladder-sparing approaches for patients with muscle-invasive bladder cancer

Matthew D. Galsky[a,b,1], Sudeh Izadmehr[a], Menggang Yu[c], Samuel D. Curtis[d,e], Christopher Douville[d,e], Maria Popoli[d,e], Janine Ptak[d,e,f], Lisa Dobbyn[d,e], Natalie Silliman[d,e,f], Kevin G. Chan[g], Tanya B. Dorff[h], Jeremy P. Cetnar[i], Brock O'Neil[j], Anishka D'Souza[k], Ronac Mamtani[l], Christos E. Kyriakopoulos[m], Rachel Brody[b,n], Evita Sadimin[o], Reza Mehrazin[p], Diego Chowell[b,q], John Sfakianos[b,p], Siamak Daneshmand[r], Sumanta K. Pal[h], Chetan Bettegowda[d,s,t], Kenneth W. Kinzler[d,e], Nickolas Papadopoulos[d,e,u], Bert Vogelstein[d,e,f,1,2], and Yuxuan Wang[d,e,2]

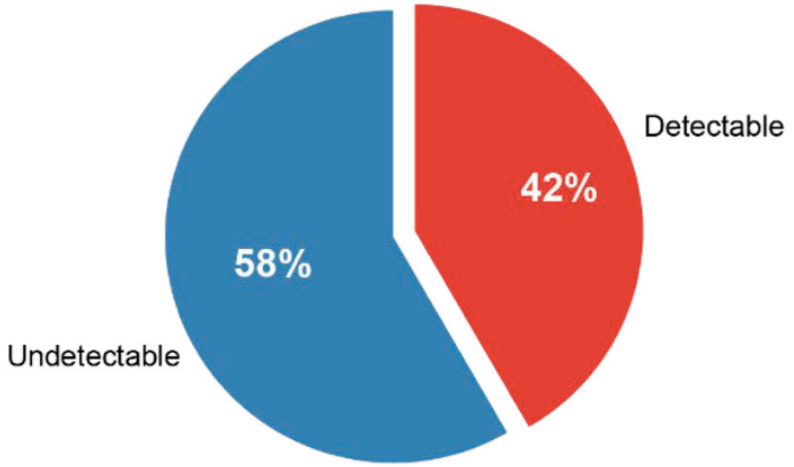
Affiliations are included on p. 7.

Contributed by Bert Vogelstein; received November 25, 2025; accepted January 8, 2026; reviewed by James M. McKiernan and Robert B. Montgomery

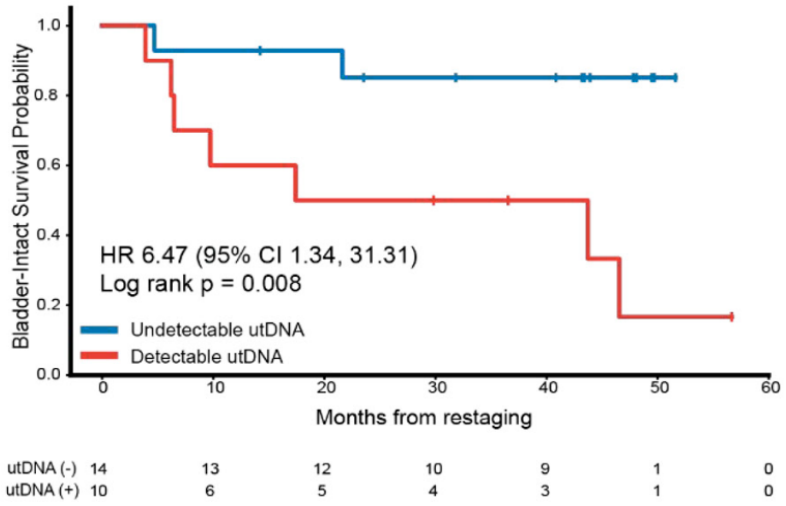
HCRN GU16-257

- +utDNA tracked local recurrence risk
  - HR 6.47; 95% CI 1.34–31.31; p = 0.008
- +ctDNA tracked metastatic risk
  - HR 4.68; 95% CI 1.10-43.35; log-rank P = 0.036
  - Only 1/22 ctDNA- patients developed a metastasis
- Neither assay was “enough” to rule out local relapse in cCR patients

utDNA Detection Frequency at Restaging Timepoint in Patients Achieving a Clinical Complete Response
(n=24)



Bladder-Intact Survival in Patients Achieving a Clinical Complete Response According to utDNA Status at Time of Restaging



So where does that leave us?

- Conceptual shift from

  “Can we will identify all relapses before they happen?”

  to

  “Can we estimate residual-disease risk well enough to make bladder preservation acceptably safe?”



So where does that leave us?

- Need to show that bladder preservation does not compromise MFS/OS
  - **Dynamic assessment, not a single time point**
    - Follow molecular status longitudinally
  - **Predefine thresholds for residual disease risk** (0%, 10%, 20%?)
    - *How much* residual-disease risk is acceptable for surveillance.
  - **Build salvage therapy into the strategy**
    - Evaluate efficacy of salvage RC or RT in cCR patients with relapse
  - **Listen to our patients and incorporate their preferences**



Summary

- Neoadjuvant therapy + RC or Concurrent chemoradiation remain the standard of care for MIBC
- Novel approaches for concurrent chemoradiation include
  - Shorter radiation: SBRT (Archer NRG-GU015)
  - Adding immunotherapy: atezolizumab (SWOG/NRG 1806)
  - Addition of EV + pembrolizumab: (EV-PRIME)
- True biomarker-guided bladder preservation is coming into focus in multiple trials: MODERN, NEO-BLAAST, EV 209, EV 309
  - MRI
  - Plasma ctDNA
  - Urinary ctDNA
  - Other emerging biomarkers

Thank you!

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