7th ANNUAL UC COURSE

Emerging personalized therapies for the management of urothelial carcinomas

7th MAY 2026
MADRID

Is bladder preservation feasible without radiotherapy?

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MY DISCLOSURES

- **Compensated Advisory Boards:**
  - MSD, BMS, Roche-Genentech, Astellas, PYCYC, IPSEN, Novartis, Bayer, Astra-Zeneca
- **Research Funding [institution]:**
  - Roche-Genentech, Astra-Zeneca
- **Cover of Travel expenses:**
  - Roche-Genentech, IPSEN, Astra-Zeneca, Bayer
- **Clinical Trials [collaboration]:**
  - BMS, Roche-Genentech, PYCYC, EISAI, MSD, Tahio Oncology, Gilead, Exelixis, Bicycle Therapeutics,
- **Compensated Lectures:**
  - EUSA pharma, MSD, BMS, Roche-Genentech, IPSEN, Jansen, Astellas, Bayer, Astra-Zeneca
- **Clinical trial [lead]:** Gilead [PI of PRISMA-1 study]

LEARNING OBJECTIVES

- Reflect about the need of bladder preserving strategies in patients with muscle invasive bladder cancer
- Review current data and discuss whether bladder preservation is feasible without radiotherapy

A **72-year-old** Spanish man, **former smoker** with a long tobacco history, presenting with **painless visible hematuria** and diagnosed with **urothelial muscle-invasive bladder cancer.**

He is **retired or near-retired man**, potentially with moderate frailty risk and probably polypharmacy.

He has **age- and smoking-related comorbidities** frequently **cardiovascular, pulmonary, renal,** or **metabolic**.

	Mortality rate, weighted average (%-range)
In-hospital mortality	2.4% (0.9–4.7)
30-day mortality	2.1% (0.0–3.7)
90-day mortality	4.7% (0.0–7.0)

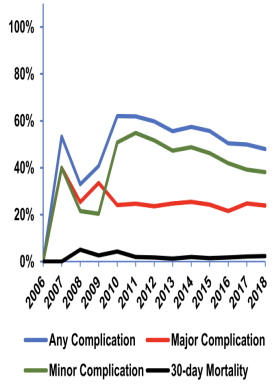


Fig. 2. Yearly complication trends.

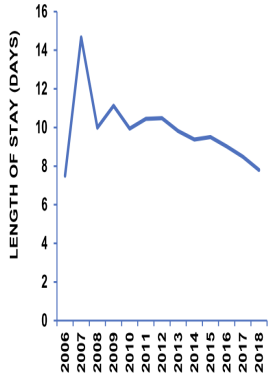
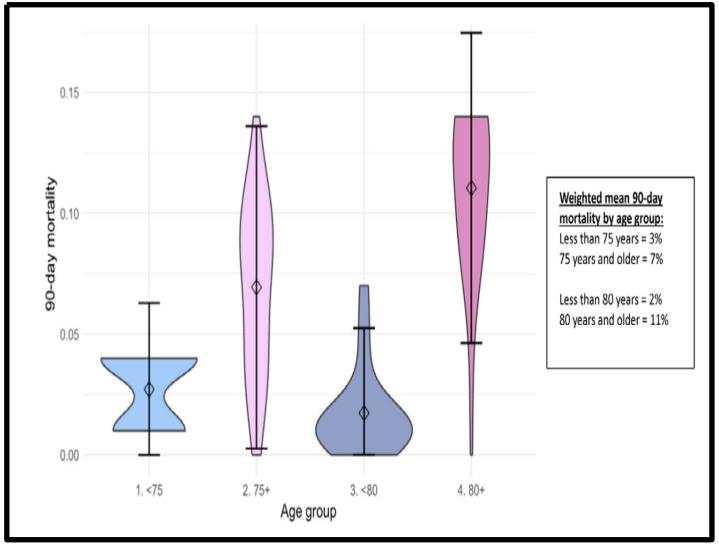


Fig. 3. Yearly mean length of stay.



Cystectomy is still an aggressive approach with relevant morbidity/mortality

Around 5% 90-day-mortality [influenced by volume/center]

Despite improvements over time some complications [i.e. infectious] remained stable and there are also long-term complications

Age is a determinant of higher complications (7% and 11% for > 75 and > 80)

Maibom SL, Joensen UN, Poulsen AM, Kehlet H, Brasso K, Røder MA. Short-term morbidity and mortality following radical cystectomy: a systematic review. BMJ Open. 2021 Apr 14;11(4):e043266 Chua KJ, Patel HV, Srivastava A, Doppalapudi SK, Lichtbroun B, Patel N, Elsamra SE, Singer EA, Jang TL, Ghodoussipour SB. Annual trends of cystectomy complications: A contemporary analysis of the NSQIP database. Urol Oncol. 2023 Sep;41(9):390.e19-390.e26. Herrera JC, Ibilibor C, Wang H, Klein GT, Elshabrawy A, Chowdhury WH, Kaushik D, Liss M, Svatek R, Mansour AM. National Trends and Impact of Regionalization of Radical Cystectomy on Survival Outcomes in Patients with Muscle Invasive Bladder Cancer. Clin Genitourin Cancer. 2020 Dec;18(6):e762-e770. doi: 10.1016/j.clgc.2020.05.012. Epub 2020 May 22. PMID: 32641262. Tempo J, Felemban S, Qin KR, Perera M, Ischia J, Bolton D, Murphy DG, Kelly B, Watson DI, O'Callaghan M. Radical cystectomy mortality in older patients: a systematic review and meta-analysis. BJU Int. 2025 Jul;136(1):19-31.

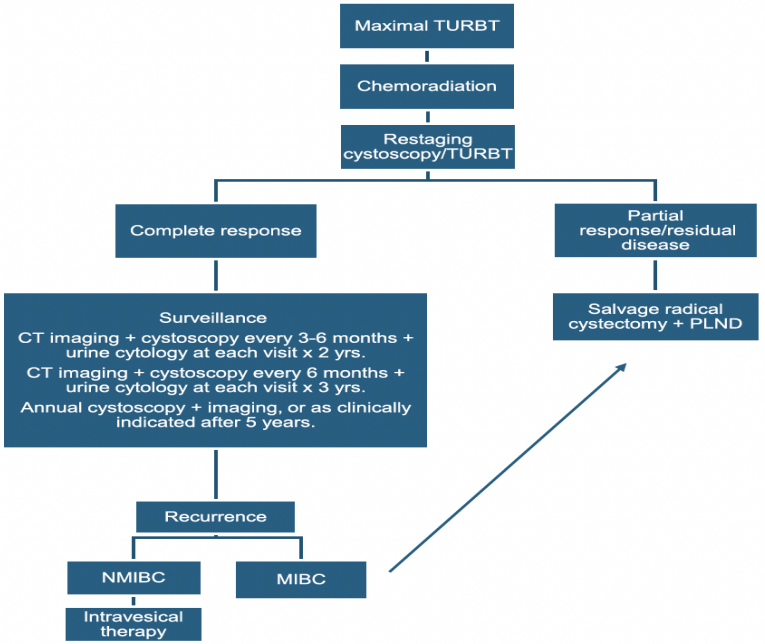
1st STATEMENT

RC is associated with substantial perioperative morbidity and long-term quality-of-life (QoL) implications

The development of safe and effective bladder-preserving strategies represents a major unmet clinical need.

Prospective trials and **pooled analyses** demonstrated that, in carefully selected patients, TMT could achieve **long- term survival** outcomes **comparable with RC**

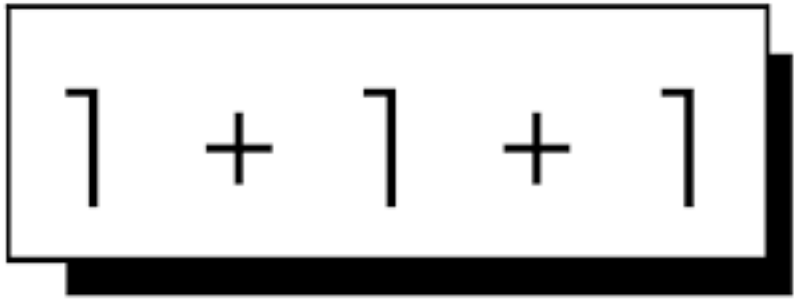
These results positioned TMT as a **valid treatment pathway** rather than an option reserved for frail or inoperable patients.



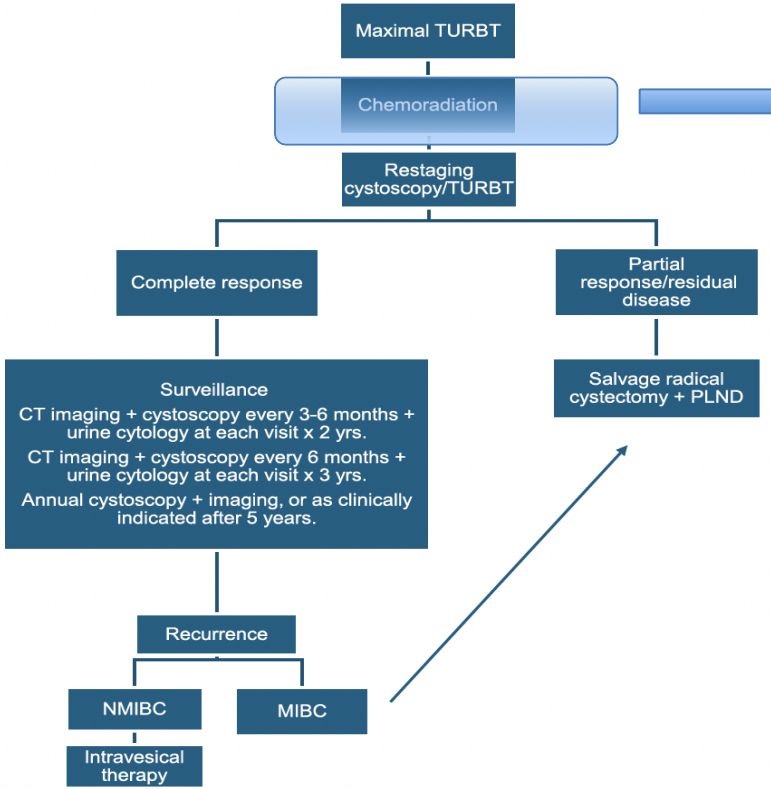
Bladder Preservation Strategies in Muscle-Invasive Bladder CancerAm Soc Clin Oncol Educ Book. 2026. Joy Li et al.

Matsukawa A, Yanagisawa T, Miszczyk M, et al: Trimodality therapy versus radical cystectomy for muscle-invasive bladder cancer: A systematic review and meta-analysis of matched cohort studies. Eur Urol Focus 11:374-385, 2025; Ben-David R, Galsky MD, Sfakianos JP: Novel bladder-sparing approaches in patients with muscle-invasive bladder cancer. Trends Mol Med 30:686-697, 2024; Zlotta AR, Ballas LK, Niemierko A et al. Lancet Oncol. 2023 Jun;24(6):669-681. Brück K, Meijer RP, Boormans JL, et al. . Int J Radiat Oncol Biol Phys. 2024 Jan 1;118(1):41-49Khetrapal, P. et al. Eur. Urol. 84, 393–405 (2023; Gupta S, et al Bladder Preservation Strategies in Muscle-invasive Bladder Cancer: Recommendations from the International Bladder Cancer Group. Eur Urol. 2026 Jan;89(1):18-28.

2ND STATEMENT: Combining strategies is the KEY for proper bladder preservation



The incorporation of **RADIATION THERAPY** with **RADIOSENSITIZING CHEMOTHERAPY** to a **TURBT** marked a pivotal advancement, establishing **TRIMODALITY THERAPY** (TMT) as the foundation of contemporary bladder preservation.



Is this becoming obsolete?

Can we bladder preserve with other means achieving equivalent/better outcomes ?

Can we skip RT while preserving the patient's bladder?

Bladder Preservation Strategies in Muscle-Invasive Bladder CancerAm Soc Clin Oncol Educ Book. 2026. Joy Li et al.

KEY QUESTIONS TO PRESERVE A BLADDER

Can we eliminate the tumor with just systemic treatment and therefore forget about consolidation [either Surgery or RT]?

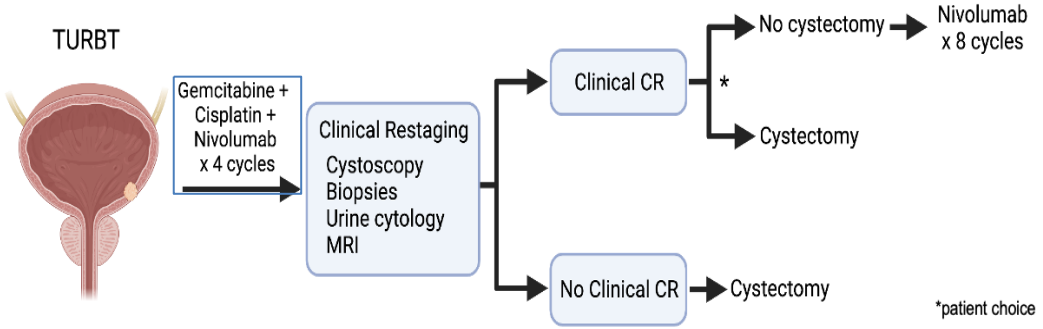
Can I treat my patients differently according to tx response ? [response-based approach]

Can I anticipate who will need more or less treatment based on tumor biology [mutation profile]?

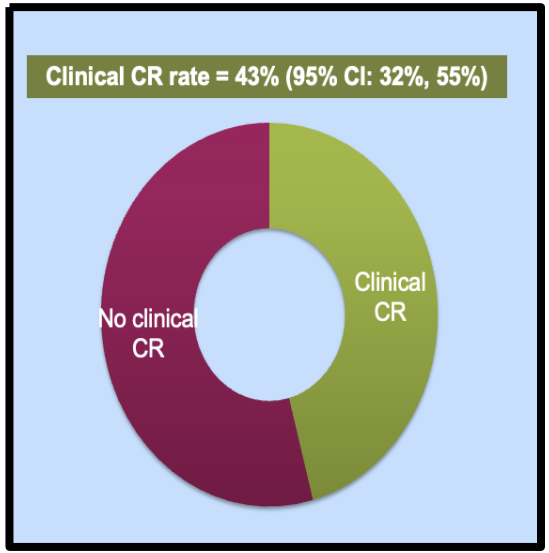
How do I define benefit in bladder preserving strategies [what is cCR]?

How can I complement the clinical/imaging information to define benefit [role of ctDNA; utDNA]?

HCRN GU16-257: Can muscle-invasive bladder cancer be treated definitively with cisplatin-based chemo + PD-1/PD-L1 blockade?

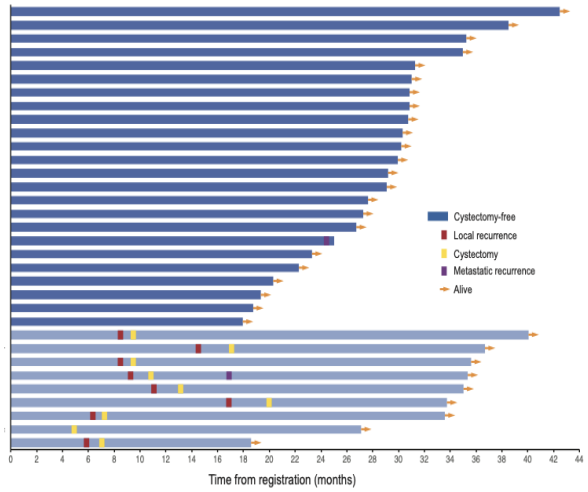


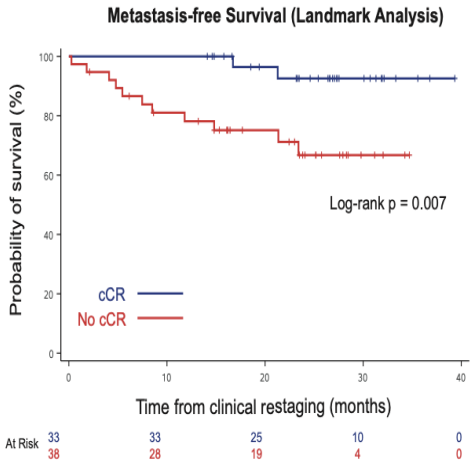
Co-primary endpoints
- Clinical complete response (CR) rate
- Performance of clinical CR in predicting treatment *benefit:*
  - 2 year metastasis free if no cystectomy
  - pCR in immediate cystectomy



Galsky MD et al. ASCO GU 2021; Galsky MD, Daneshmand S, Izadmehr S, et al. **Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer: a phase 2 trial.** *Nature Medicine.* 2023;29:2825–2834.

Outcomes of patients achieving a clinical CR





PPV of cCR for 2y-MFS 0.97.

The study **supports feasibility of response-adapted bladder preservation but..** remains investigational pending randomized validation and longer follow-up

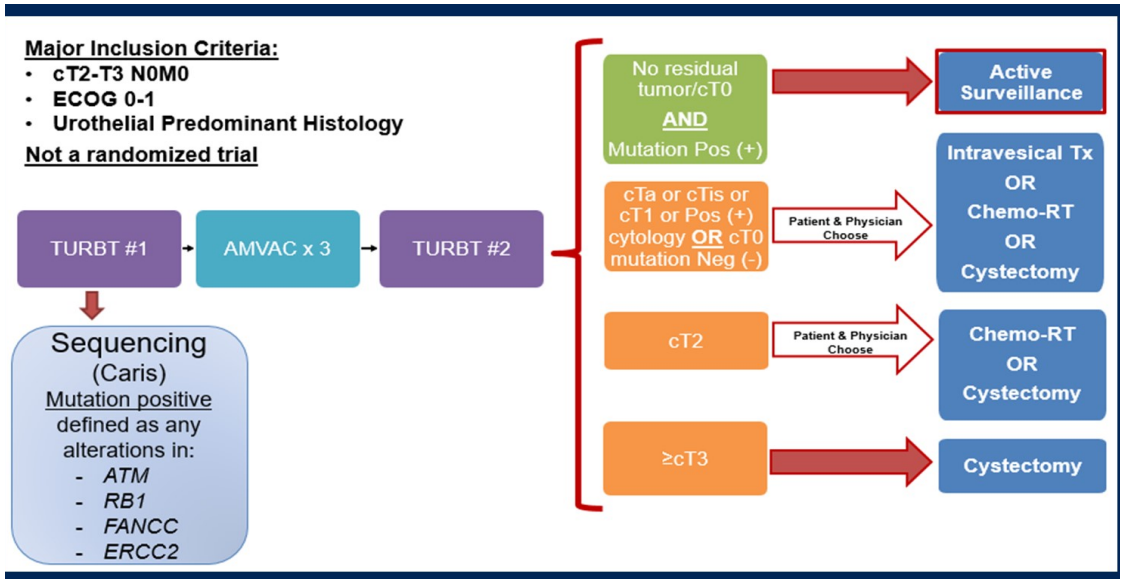
Mutations in *ERCC2*, *FANCC*, *RB1*, or *ATM* did not improve PPV beyond CCR alone

Positive predictive value of clinical CR for 2 year MFS: 0.97 (95% CI: 0.91, 1)

Galsky MD et al. ASCO GU 2023: Galsky MD, Daneshmand S, Izadmehr S, et al. **Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer: a phase 2 trial.** *Nature Medicine.* 2023;29:2825–2834.

We know that “classic” cisplatin-based chemotherapy can achieve a pCR in about 35-50% of the patients.
Can we anticipate patients that will benefit MORE and do a RISK based approach? Can I transfer data from mUC?

Risk Enabled Therapy After Initiating Neoadjuvant CHEMOTHERAPY (RETAIN STUDY)

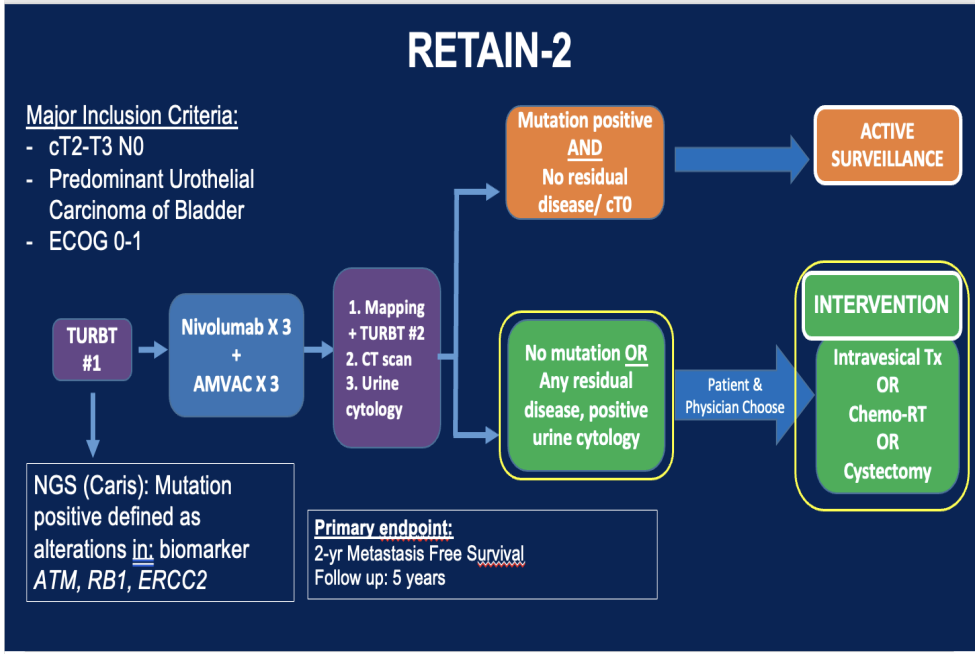


- A single-arm, phase II, **noninferiority trial** to evaluate **a RISK ADAPTED APPROACH**
- The PRIMARY END POINT was **METASTASIS-FREE SURVIVAL** at 2 years for the entire cohort

- 70 patients; 33/70 (47%) had a qualifying mutation, and 25/70 (36%) entered active surveillance.
- 2-year MFS 73%; 2 Y OS 84.3% [trial **DID NOT MEET** its primary noninferiority endpoint]

•Daniel M. Geynisman et al. Phase II Trial of Risk-Enabled Therapy After Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer (RETAIN 1). *J Clin Oncol* **43**, 1113-1122(2025)

What if we improve the regime?

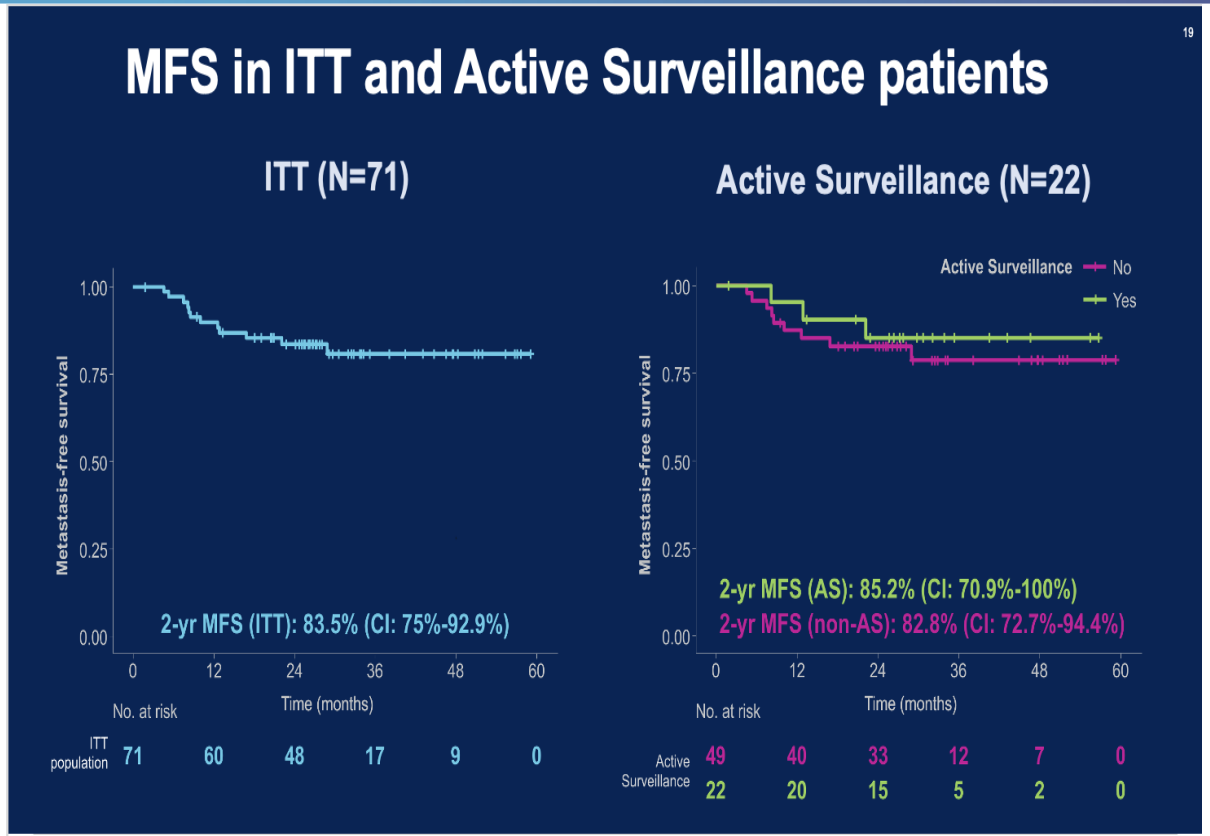


Patient Characteristics (N=71)

Characteristic		n	(%)
Age, years	Median	69	–
	Range	68–86	–
Gender	Male	55	77%
	Female	16	23%
ECOG Performance Status	0	57	80%
	1	14	20%
Histology	Pure UC	48	68%
	UC/Variant histology	23	32%
Clinical Stage	cT2	41	58%
	cT3	30	42%
Mutation Status	Positive	31	44%
	Negative	40	56%

- **Primary Objective:** To evaluate whether the risk-adapted strategy is non-inferior to standard-of-care neoadjuvant chemotherapy followed by cystectomy for all patients
- Slightly different statistical assumptions than RETAIN-1

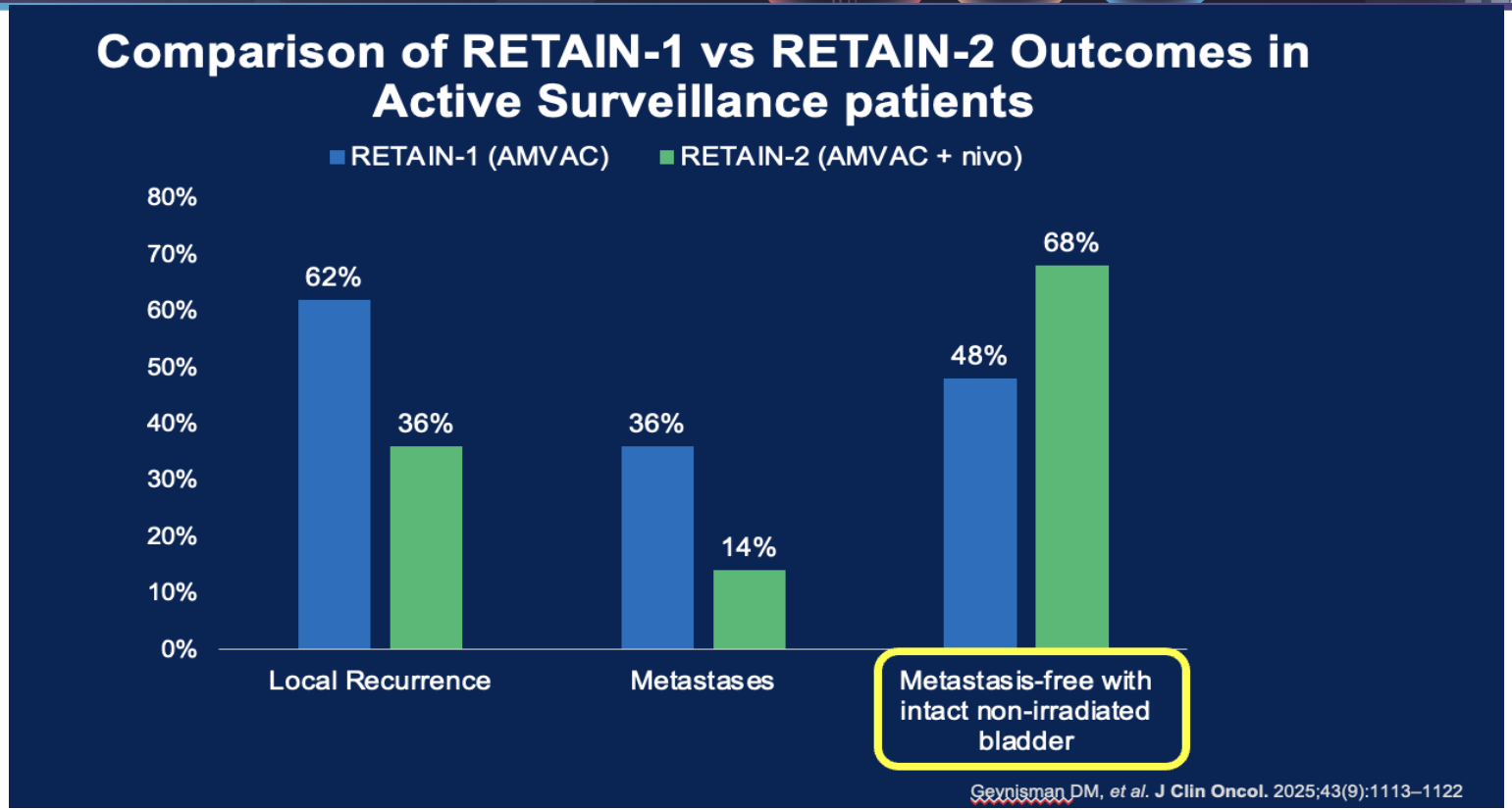
Ghatalia P, et al. **A phase 2 trial of risk-enabled therapy after neoadjuvant chemo-immunotherapy for muscle-invasive bladder cancer: RETAIN-2.** *J Clin Oncol.* 2025;43(suppl 5):815. ASCO GU 2025. Ghatalia P, Geynisman DM, Plimack ER, et al. Circulating tumor DNA (ctDNA) to guide response-adapted bladder preservation in muscle-invasive bladder cancer (MIBC): Integrated analysis of the RETAIN trials. J Clin Oncol. 2026;44(suppl 7):LBA632. ASCO GU 2026.



- The proportion of patients who were **metastasis-free at 2 years for ITT was 70%** with the lower bound of 1-sided 90% exact CI of 62.4%

- Non-inferiority declared if lower bound of 1-sided 90% exact CI > 56%

Ghatalia P, et al. **A phase 2 trial of risk-enabled therapy after neoadjuvant chemo-immunotherapy for muscle-invasive bladder cancer: RETAIN-2.** *J Clin Oncol.* 2025;43(suppl 5):815. ASCO GU 2025. Ghatalia P, Geynisman DM, Plimack ER, et al. Circulating tumor DNA (ctDNA) to guide response-adapted bladder preservation in muscle-invasive bladder cancer (MIBC): Integrated analysis of the RETAIN trials. J Clin Oncol. 2026;44(suppl 7):LBA632. ASCO GU 2026.

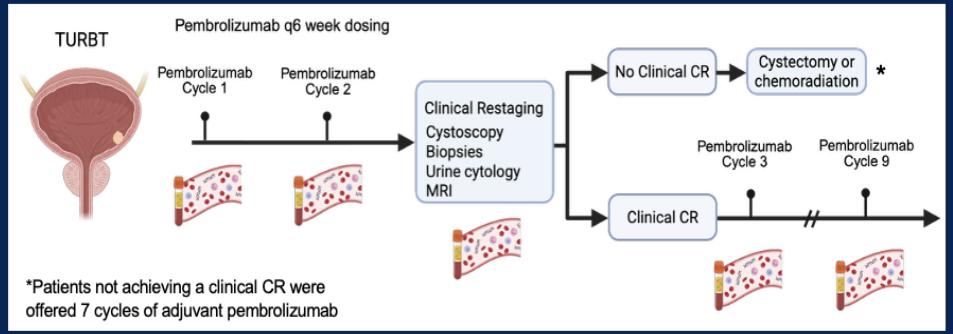


Ghatalia P, et al. **A phase 2 trial of risk-enabled therapy after neoadjuvant chemo-immunotherapy for muscle-invasive bladder cancer: RETAIN-2.** *J Clin Oncol.* 2025;43(suppl 5):815. ASCO GU 2025. Ghatalia P, Geynisman DM, Plimack ER, et al. Circulating tumor DNA (ctDNA) to guide response-adapted bladder preservation in muscle-invasive bladder cancer (MIBC): Integrated analysis of the RETAIN trials. J Clin Oncol. 2026;44(suppl 7):LBA632. ASCO GU 2026.

What if my patient can not receive cisplatin-based NAC?

HCRN GU20-444

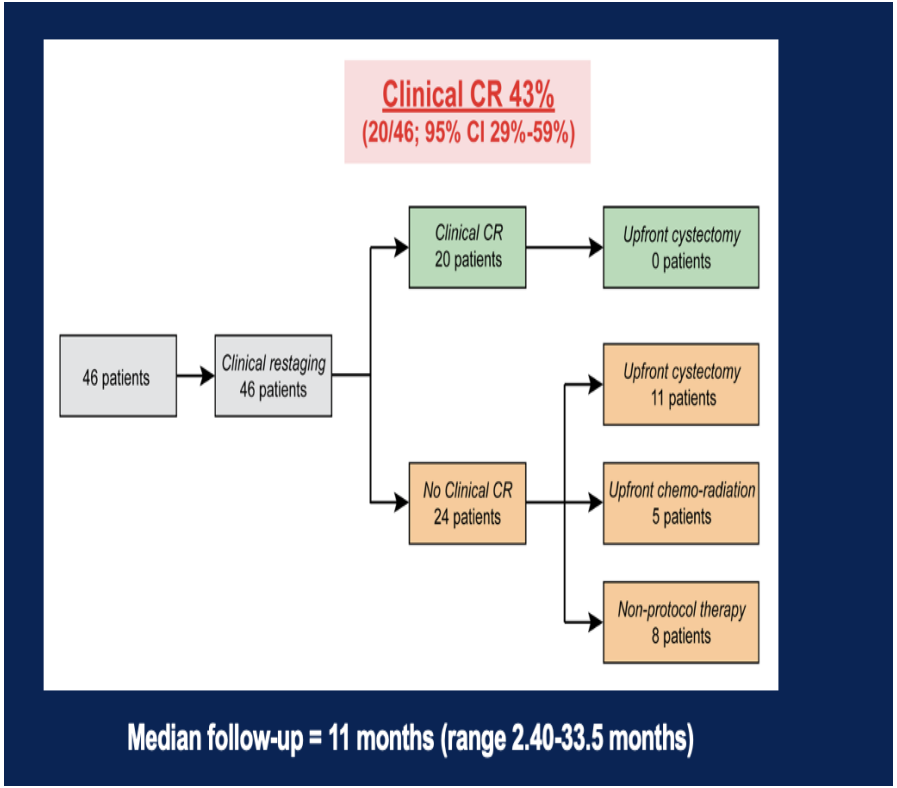
Eligibility:
- cT2-3N0M0 urothelial cancer of the bladder
- Declined or ineligible for cisplatin
- Creatinine clearance ≥30 mL/min



Primary endpoints
- Clinical CR rate
- 2-year metastasis-free survival in patients achieving a clinical CR and omitting upfront cystectomy

Key Secondary endpoints
- Safety, 2-year metastasis-free survival, bladder-intact event-free survival, overall survival

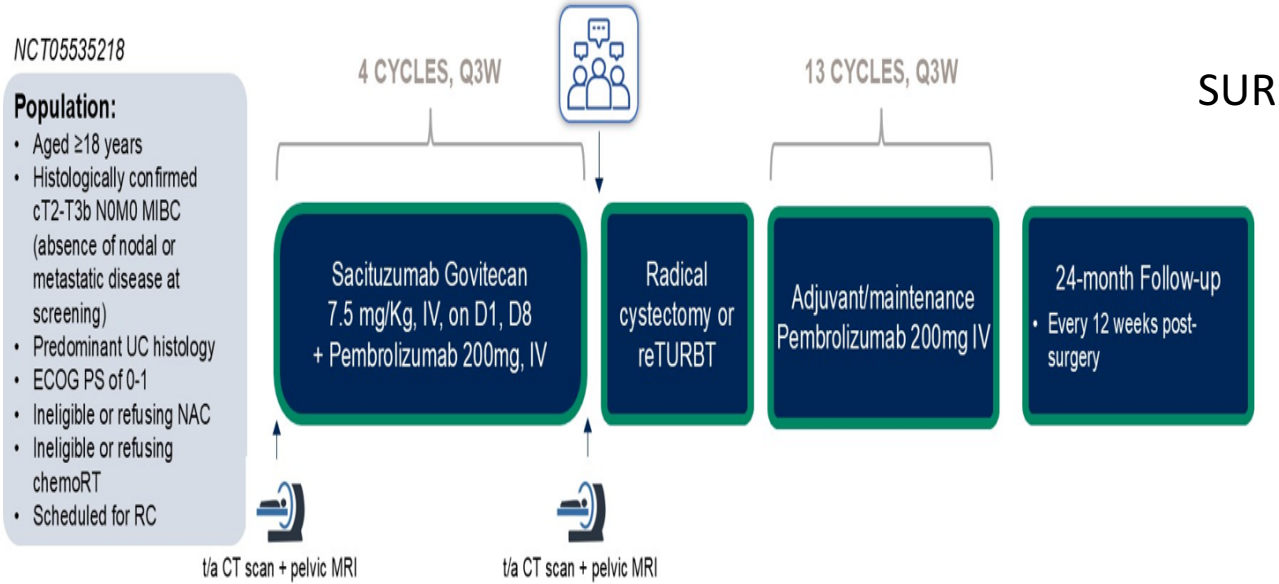
Anker JF, King J, Tripathi A, et al. **Phase 2 trial of pembrolizumab with response-guided bladder-sparing in patients with muscle-invasive bladder cancer (MIBC; HCRN GU 20-444).** *J Clin Oncol.* 2026;44(suppl 7):737. ASCO GU 2026 abstract.



A uniformly assessed and stringently defined clinical CR was achieved in **43%** of patients treated with pembrolizumab monotherapy after TURBT and facilitated a response-guided bladder-sparing approach.

Anker JF, King J, Tripathi A, et al. **Phase 2 trial of pembrolizumab with response-guided bladder-sparing in patients with muscle-invasive bladder cancer (MIBC; HCRN GU 20-444).** *J Clin Oncol.* 2026;44(suppl 7):737. ASCO GU 2026 abstract.

SURE-02



- 49 pts were treated and efficacy evaluable.
- 33 (67.3%) had a cT2 stage, 19 (38.8%) had a centrally confirmed variant histology.
- The **cCR-rate was 38.8% ,** all these pts underwent a reTURBT; ypT≤1N0-x rate was 51%
- EFS 71% 12m **EFS in cCR was 91%** vs 59.6% in non-cCR

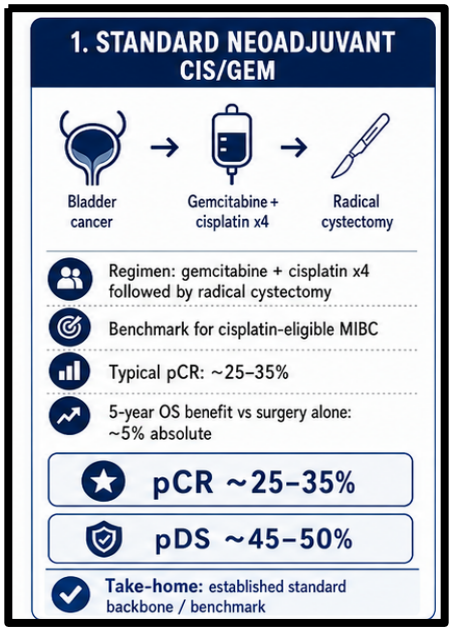
Necchi A, et al. **Neoadjuvant sacituzumab govitecan plus pembrolizumab followed by response-adapted bladder sparing and adjuvant pembrolizumab in patients with muscle-invasive bladder cancer: SURE-02 primary analysis and biomarker results.** *J Clin Oncol.* 2026;44(suppl 7):769. ASCO GU 2026.

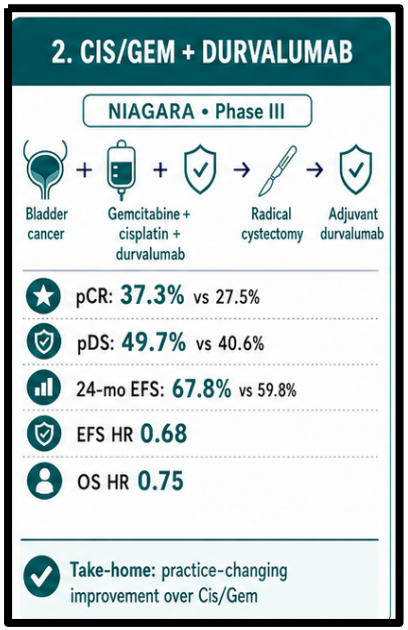
3rd STATEMENT

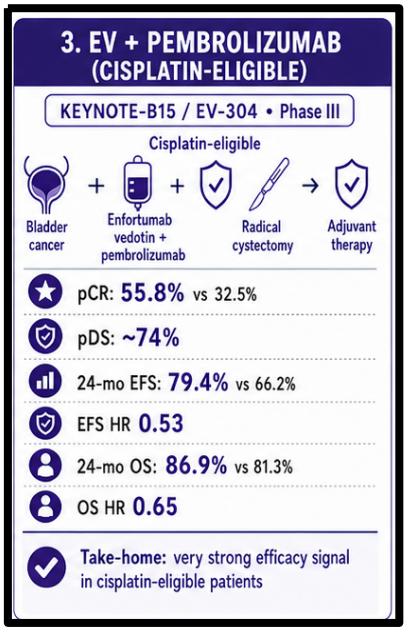
Response-adapted bladder preservation after NAC or chemoimmunotherapy is promising with cCR in about 30-45% of the patients and favorable 2y-MFS but evidence is limited and within small clinical trials

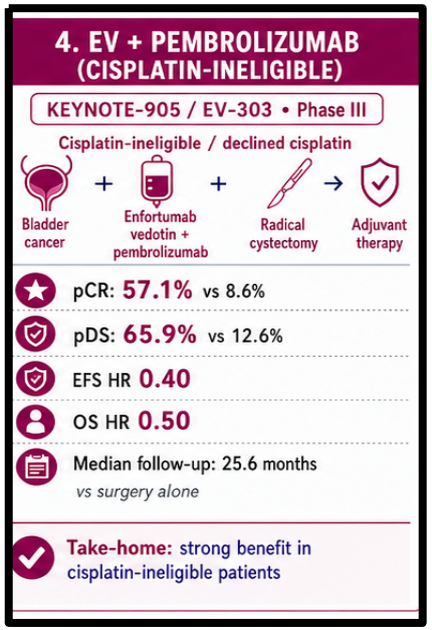
What is next?

What if we used the best/most recent therapies in the perioperative setting?



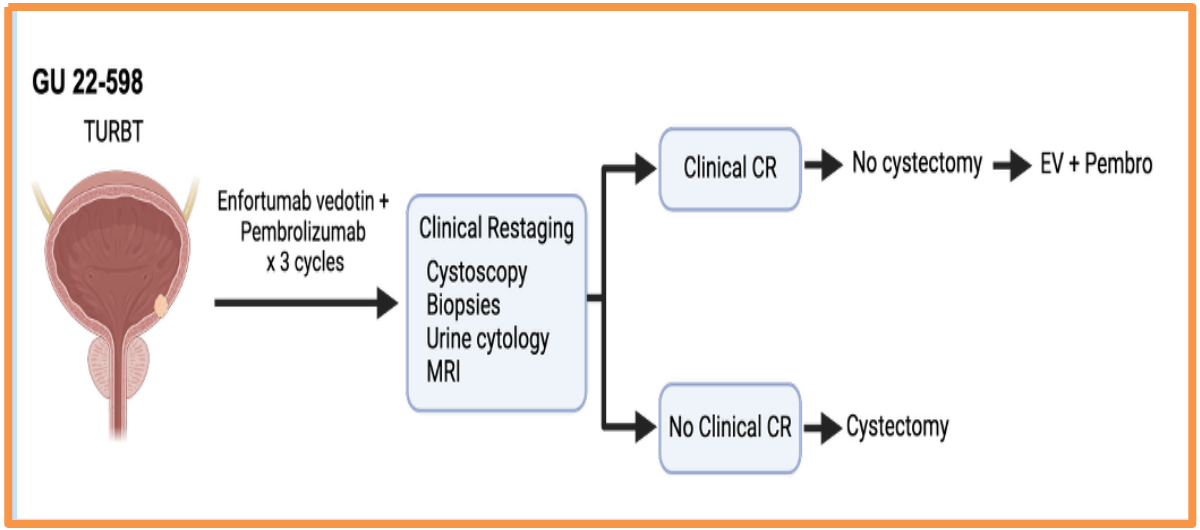






With **modern perioperative systemic strategies combining cytotoxics + I.O** about **2 thirds** of patients **achieve a pCR** and around **65-75% a downstaging**

Hoosier Cancer Research Network



A **single-arm, multicenter phase II trial** evaluating whether EV+ P can induce a stringent **clinical complete response** in localized **cT2–T3N0M0 MIBC**, allowing selected patients to avoid upfront cystectomy.

Planned sample size **47 patients.** The study is enrolling at **5 institutions** [ASCO GU 2026 TPS abstract]

Miller EJ, et al. 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. J Clin Oncol. 2026;44(suppl 7):TPS891. ClinicalTrials.gov: NCT06809140..

KEY QUESTIONS TO PRESERVE A BLADDER

Can we eliminate the tumor with just systemic treatment and therefore forget about consolidation [either Surgery or RT]?

Can I treat my patients differently according to tx response ? [response-based approach]

Can I anticipate who will need more or less treatment based on tumor biology [mutation profile]?

How do I define benefit in bladder preserving strategies [what is cCR]?

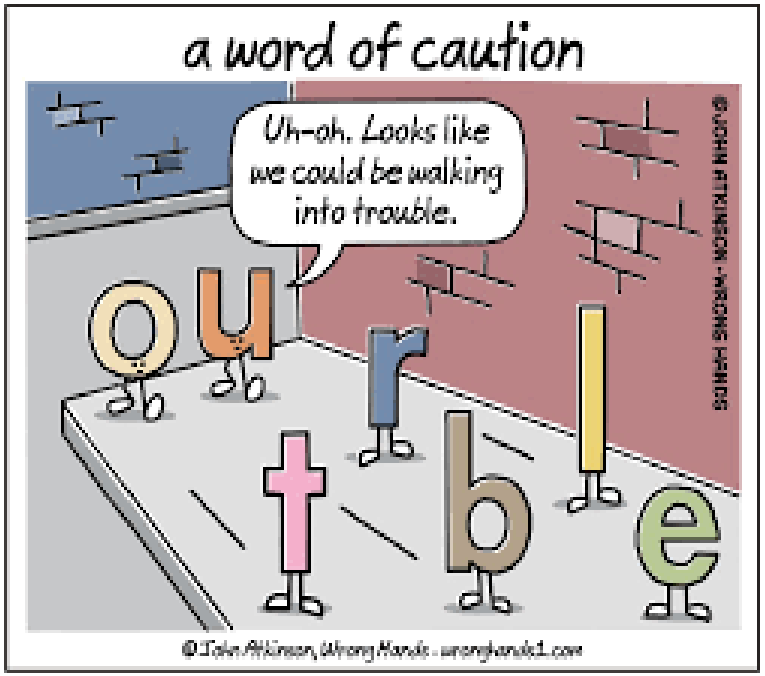
How can I complement the clinical/imaging information to define benefit [role of ctDNA; utDNA]?

All the previous studies based their decisions on response

[complete clinical response. (cCR)]

Is this a homogenous concept?

Has cCR been validated in large series?



cCR in MIBC bladder-preservation trials is defined as a composite endpoint:

1.- NO visible tumor on **CYSTOSCOPY**

2.- Negative tumor-bed/template **biopsY**

3.- **Re-TURBT,** negative

4.- Negative **URINE CYTOLOGY**

5.- No disease on **IMAGING** (local, nodal, or metastatic)

- cCR is **not equivalent to pCR**. It can miss residual invasive disease, CIS, or local field recurrence.
- It is NOT defined homonogenously across trials
- Therefore, cCR-based bladder preservation should require **strict surveillance and immediate access to salvage cystectomy or chemoradiation**

KEY QUESTIONS TO PRESERVE A BLADDER

Can we eliminate the tumor with just systemic treatment and therefore forget about consolidation [either Surgery or RT]?

Can I treat my patients differently according to tx response ? [response-based approach]

Can I anticipate who will need more or less treatment based on tumor biology [mutation profile]?

How do I define benefit in bladder preserving strategies [what is cCR]?

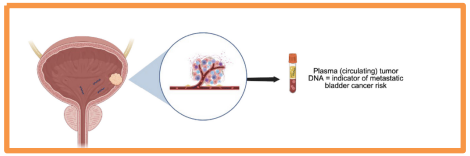
How can I complement the clinical/imaging information to define benefit [role of ctDNA; utDNA]?

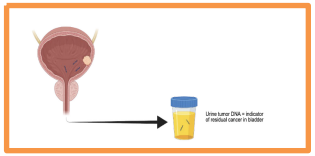
Do we have any other means to complement decisions in RT Free-bladder preserving strategies?

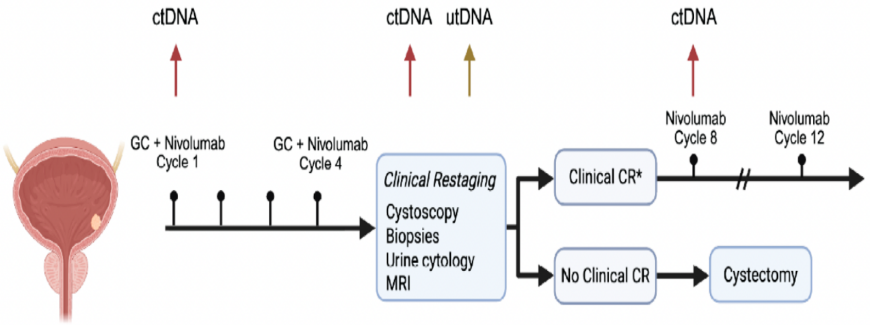

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES OPEN ACCESS

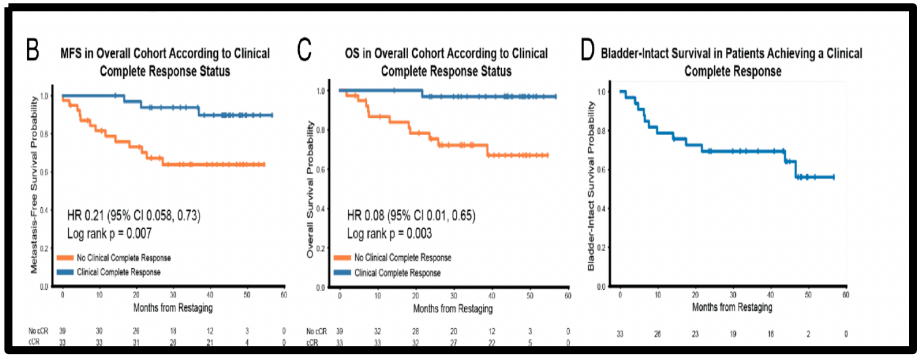
Monitoring of plasma and urine tumor-derived DNA to inform bladder-sparing approaches for patients with muscle-invasive bladder cancer

Matthew D. Galsky[a,b,1], Sudeh Izadmehr[a], Menggang Yu[c], Samuel D. Curtis[a,b], Christopher Douville[d,e], Maria Popoli[d,e], Janine Ptak[d,e], Lisa Dobbyn[d,e], Natalie Silliman[d,e], Kevin G. Chan[d], Tanya B. Dorff[f], Jeremy P. Cetnar[f], Brock O'Neil[f], Anishka D'Souza[f], Ronac Mamtani[f], Christos E. Kyriakopoulos[a,b], Rachel Brody[a,b], Evita Sadimin[a], Reza Mehrazin[g], Diego Chowell[h,i], John Sfakianos[g,h], Siamak Daneshmand[j], Sumanta K. Pal[k], Chetan Bettegowda[l,m], Kenneth W. Kinzler[d,e], Nickolas Papadopoulos[d,e,n], Bert Vogelstein[d,e,o,2], and Yuxuan Wang[d,e,2]

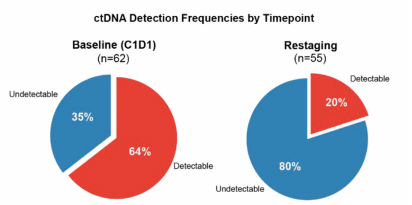


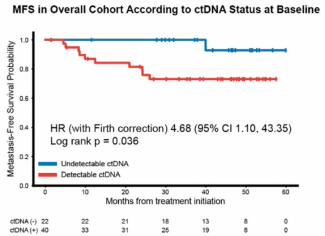


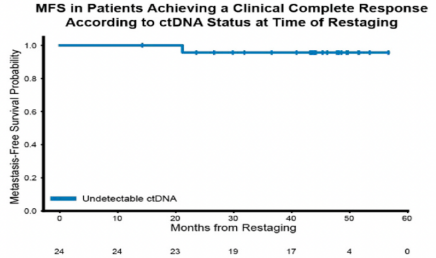


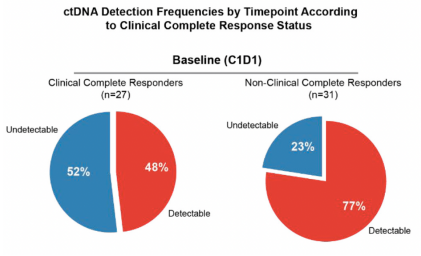


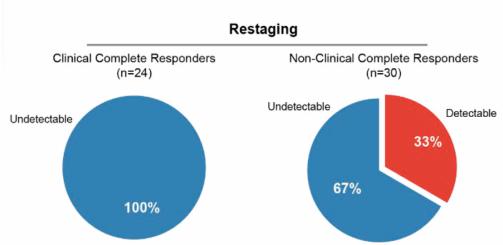
- Three-year bladder-intact survival among patients with a complete clinical response following four rounds of systemic therapy was 69%.
- However, **a subset of patients omitting initial cystectomy developed recurrence** highlighting the need for biomarkers to refine patient selection

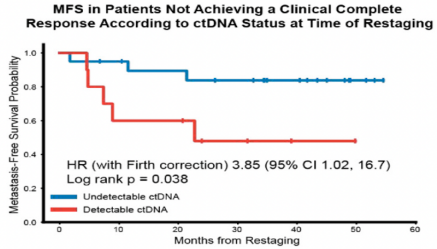






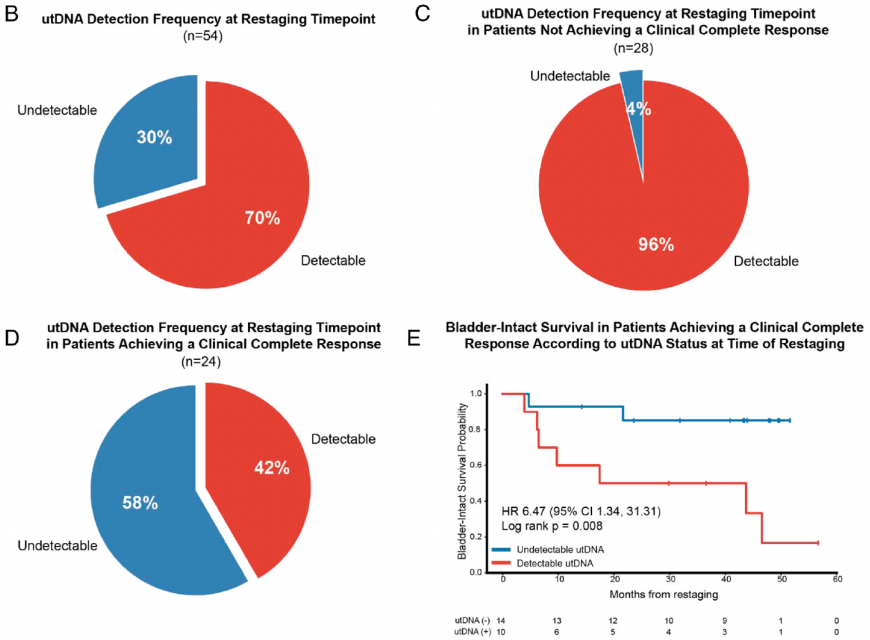


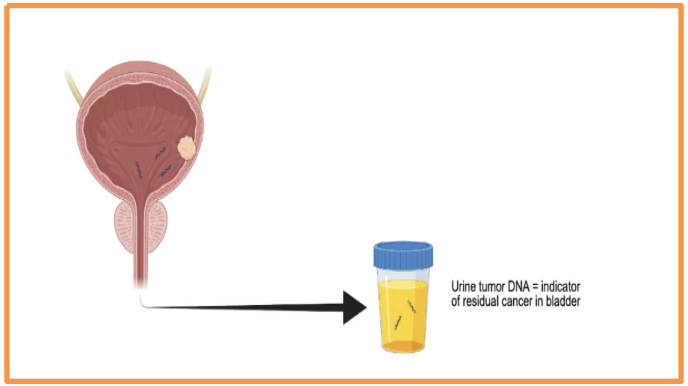




- Metastatic risk was significantly higher for patients with detectable versus undetectable ctDNA presystemic therapy (HR 4.68; 95% CI 1.10-43.35; log-rank *P* = 0.036).

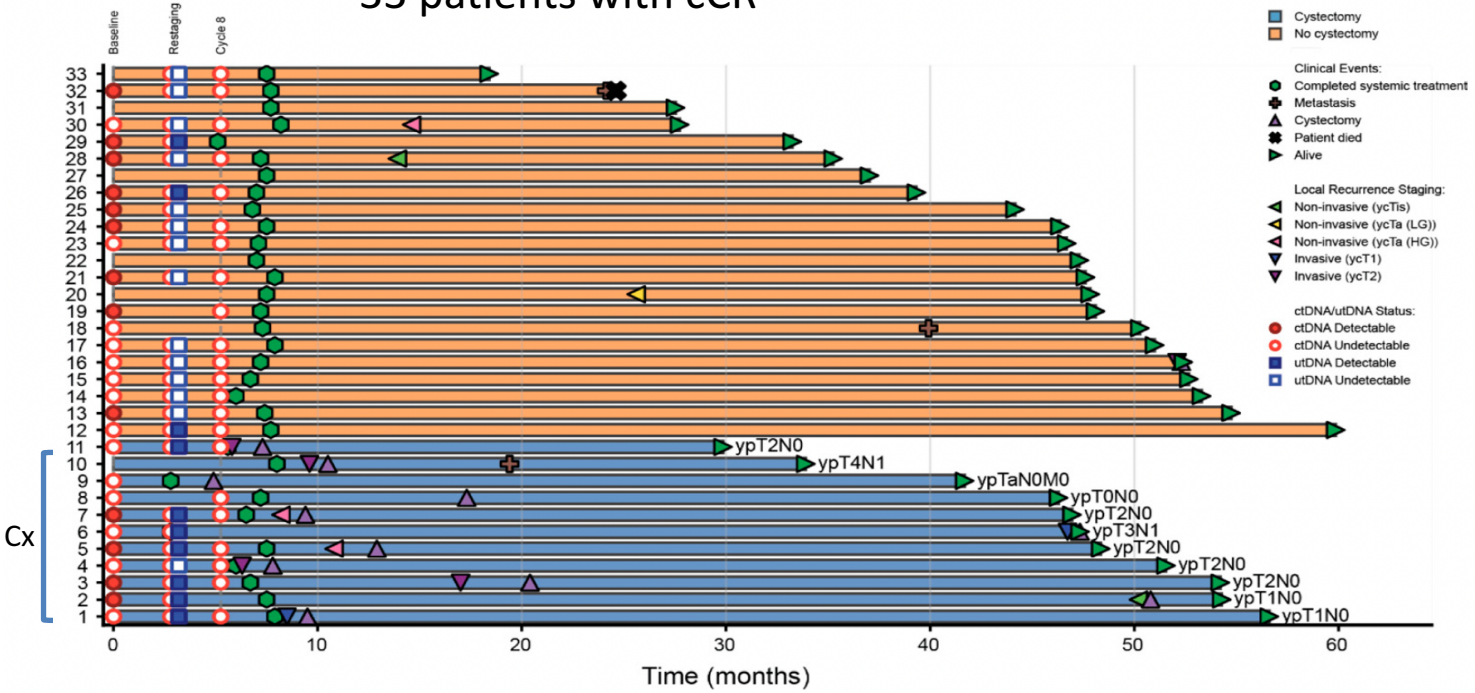
- Only 4.5% (1 of 22) of patients with undetectable baseline ctDNA developed metastatic disease. Undetectable ctDNA before or after systemic therapy was associated with extremely low metastatic risk





- There was a **difference in utDNA** detectability between patients who did versus did not achieve a **cCR** (40% and 96%, respectively; P < 0.0001
- **Detectable urine utDNA** in patients with a complete clinical response was **associated with shorter bladder-intact survival** (HR 6.47, 95% CI 1.34-31.31; log-rank *P* = 0.008).

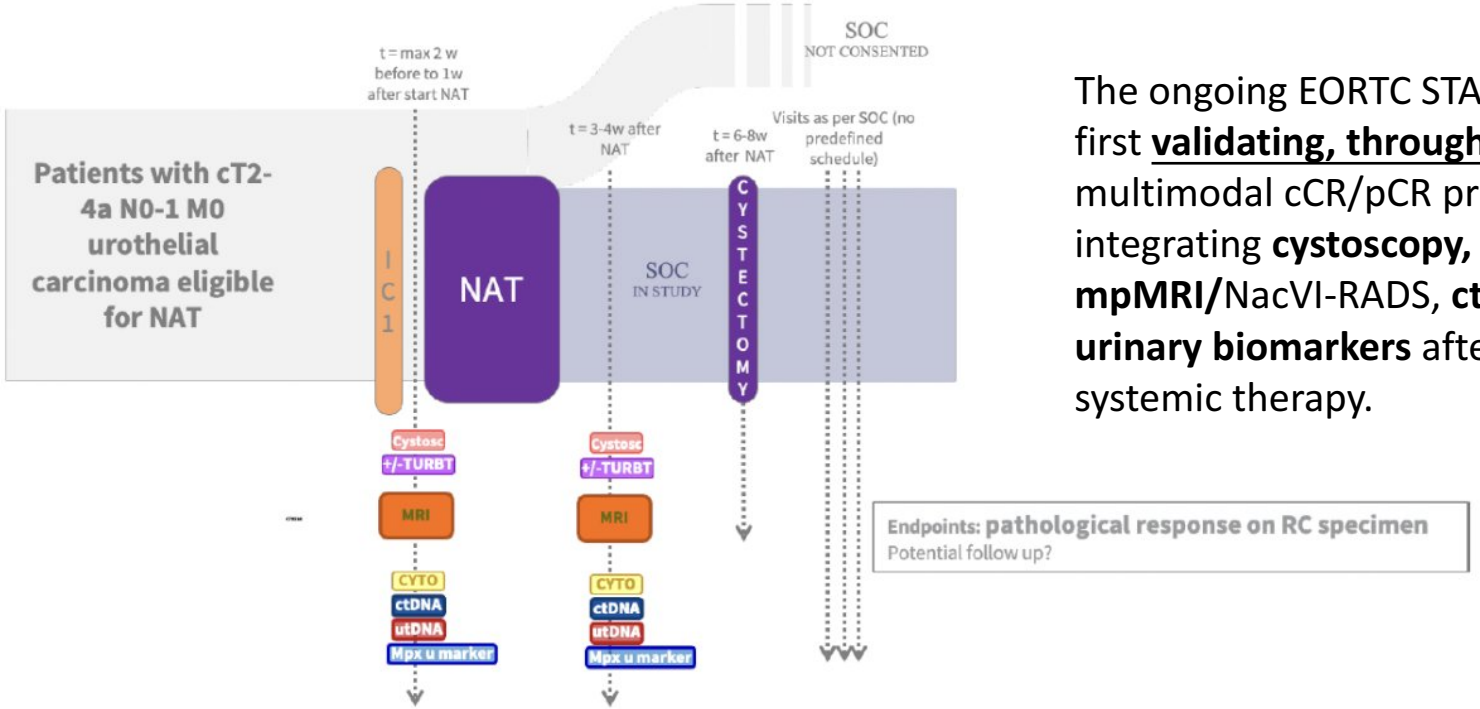
33 patients with cCR



Among 33 patients with a cCR, **high-grade recurrences in the bladder** occurred in 70% (7/10) with detectable utDNA at restaging and 29% (4/14) with undetectable utDNA at restaging.

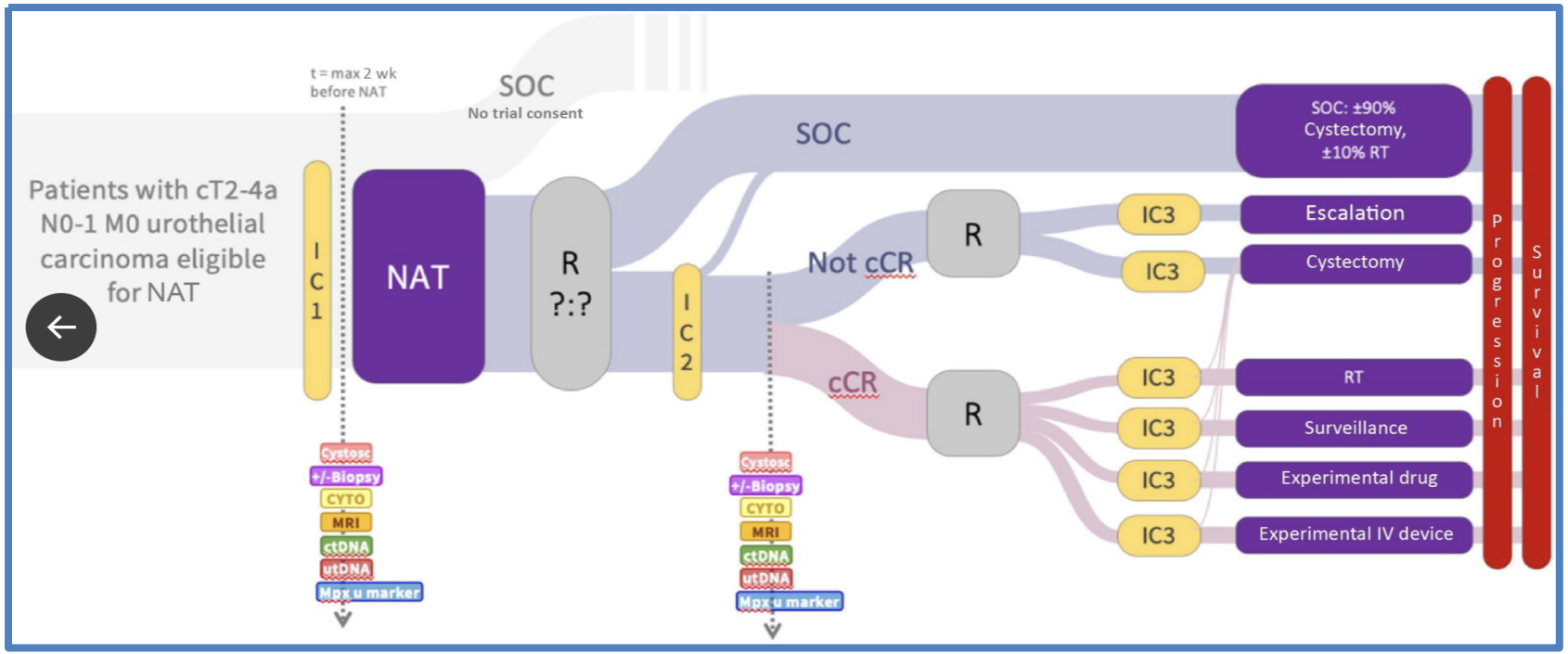
4th STATEMENT

utDNA refines local response assessment by detecting residual intravesical disease while ctDNA provides complementary systemic risk stratification, identifying patients at higher risk of occult metastatic disease



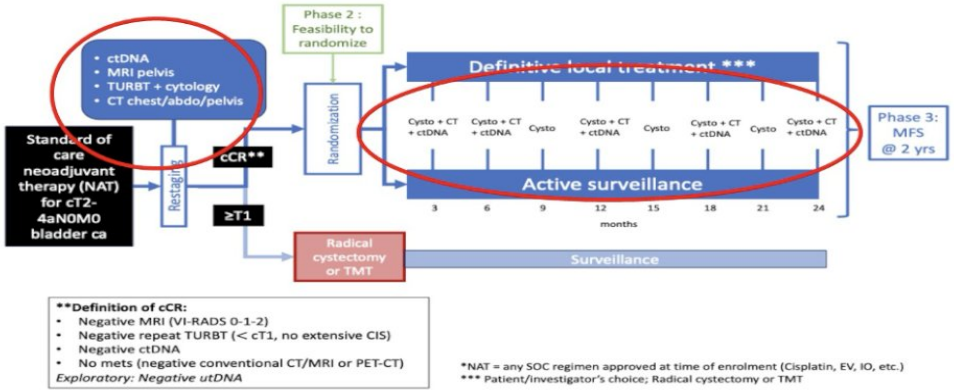
The ongoing EORTC STARBURST program is first **validating, through STARBURST-1**, a multimodal cCR/pCR prediction signature integrating **cystoscopy, cytology, mpMRI/**NacVI-RADS, **ctDNA**, **utDNA**, and **urinary biomarkers** after neoadjuvant systemic therapy.

Grisay G, et al. **EORTC GUCG 2418 — STARBURST: Strategies for Treatment Adaptation Following Re-Evaluation of the Bladder After Using Primary Neoadjuvant Systemic Therapies.** *J Clin Oncol.* 2025;43(suppl 5):TPS880.



If validated, this signature will feed into STARBURST-2, a phase III response-adapted strategy trial testing de-escalation/bladder preservation in responders and escalation in non-responders.

NEO-BLAST
Neoadjuvant therapy for bladder cancer followed by active surveillance vs definitive treatment



N=688

PI: St Laurent
NCT06537154
Trial in progress

NEO-BLAST / NCT06537154: Phase II/III randomized response-adapted trial in MIBC. After NAT, patients with cCR—defined by negative ctDNA, negative bladder MRI, and negative repeat TURBT—are randomized to **active surveillance** versus **definitive bladder treatment** with radical cystectomy or chemoradiation.

The primary outcome will be **2-year metastasis free survival** for patients with clinical complete response managed with active surveillance versus definitive bladder treatment. Secondary outcomes will be bladder intact event free survival, overall survival, treatment acceptance rates, and quality of life.

NEO-BLAST: Neoadjuvant therapy for bladder cancer followed by active surveillance vs treatment. ClinicalTrials.gov: **NCT06537154**. Presented as trial-in-progress: *J Clin Oncol.* 2025;43(suppl 5):TPS890; ASCO GU 2025.

7th ANNUAL UC COURSE

Emerging personalized therapies for the management of urothelial carcinomas

7th MAY 2026
MADRID

Is bladder preservation feasible without radiotherapy?

Ignacio Duran, MD, PhD
Hospital Universitario Marques de Valdecilla. IDIVAL
Santander

WITH A HIGH LEVEL OF EVIDENCE NOT TODAY…BUT MOST LIKELY SOON

GRACIAS POR VUESTRA ATENCION

Bladder preservation without radiotherapy is feasible in highly selected patients — particularly those with unifocal cT2 tumors achieving clinical complete response to neoadjuvant systemic therapy — but it remains investigational and not yet guideline-endorsed as a standard approach.

Current guidelines uniformly recommend chemoradiotherapy as the backbone of bladder preservation.

Emerging data from response-adapted chemotherapy ± immunotherapy trials (HCRN GU16-257, RETAIN, SURE-02) and long-term TURBT + chemotherapy data (Donat 2025) are promising but require longer follow-up and phase 3 validation before they can replace radiation-based strategies.

NOT ALL THE STUDIES CONSIDERED cCR EXACTLY THE SAME

STUDY	cCR DEFINITION USED OR IMPLIED
RETAIN-1/2 [MVAC/NIVO]	**cT0 after NAC**, with no clinical evidence of disease by **restaging TURBT, urine cytology, and imaging**, plus favorable DDR mutation profile.
HCRN GU16-257 [CIS-GEM-NIVO]	Clinical restaging included **MRI abdomen/pelvis , CT chest, cystoscopy** with **template biopsies,** and **urine cytology**.
HCRN GU20-444 [PEMBRO]	Restaging **MRI/CT, urine cytology, cystoscopy, and biopsies**.
HCRN GU22-598 [EV-P]	cCR is described as a **stringently defined composite endpoint** based on **bladder MRI, urine cytology, cystoscopy, and biopsies/TURBT**.
SURE-02 [SG-PEMBO]	cCR for bladder-sparing patients was defined as **negative imaging plus no viable tumor at repeat TURBT**.

Definitions vary across trials, and cCR should be considered a risk-stratification tool—not proof of eradication.