Chemo plus immunotherapy as a strategy to preserve bladders: current evidence and future perspectives?

Dr. Elena Sevillano, Medical Oncology Department, Centro Integral Oncológico Clara Campal HM CIOCC, Madrid

THE CURRENT STANDARD OF CARE FOR MIBC IS A BIG DEAL

Each modality is associated with long-term toxicity

We need to de-intensify while maintaining outcomes!

CRITICAL CHALLENGES OF BLADDER PRESERVATION (BP)

1. **Could we safely omit local therapy?**
   - Cystectomy, Radiotherapy

2. **Could we better select patients for BP?**
   - Predictive and prognostic biomarkers

3. **Do we have rigorous methods to measure and define clinical complete response?**

4. **Can more efective systemic therapy increase BP rates?**
   - IO, ADC

CRITICAL CHALLENGES OF BLADDER PRESERVATION (BP)

1. **Could we safely omit local therapy?**
   - Cystectomy, Radiotherapy

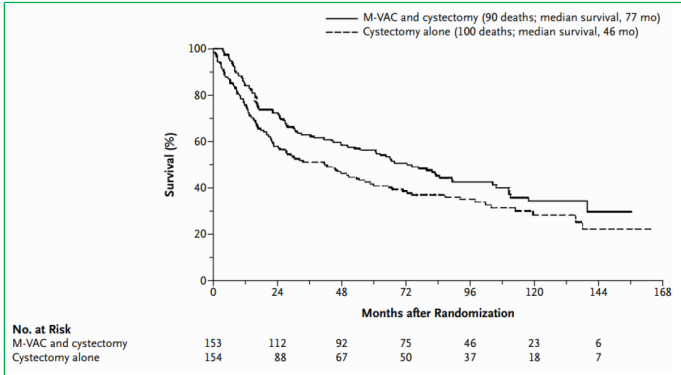
RADICAL CYSTECTOMY:

- A major/complex operation
- Risk of perioperative morbidity & mortality : 1.5% (older age, smokers, comorbidities)
- Frequent complications: 30-60%
- Loss of normal bladder function
- Requires urinary diversion
- Urinary & sexual dysfunction
- Profound impact on QOL (patient´s preference to retain their bladder)

Rose B, ASCO 2023. Galsky,M Nat Medicine 2023

A pathological CR is achieved in 30-40% of patients with cisplatin-based NAC for MIBC and is associated with favorable outcomes

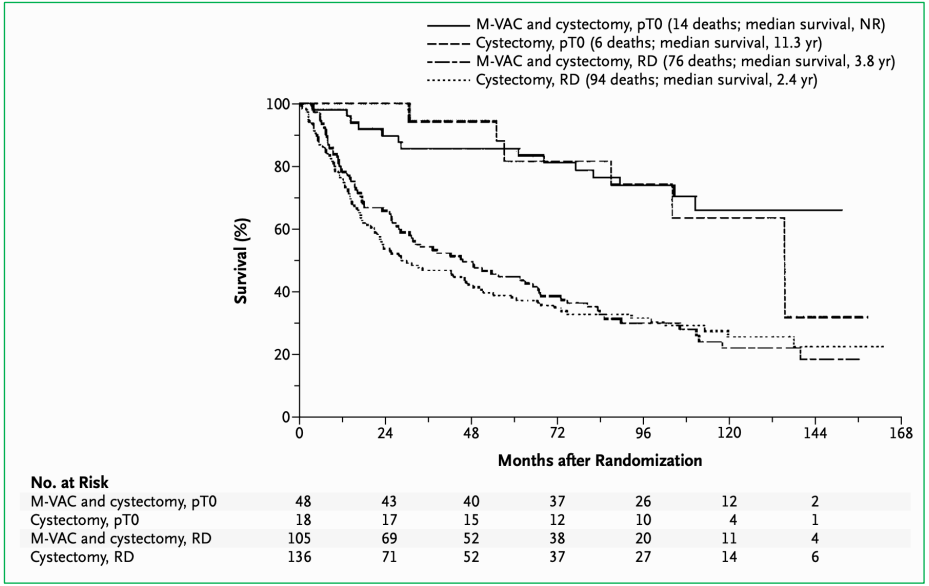
SWOG-8710



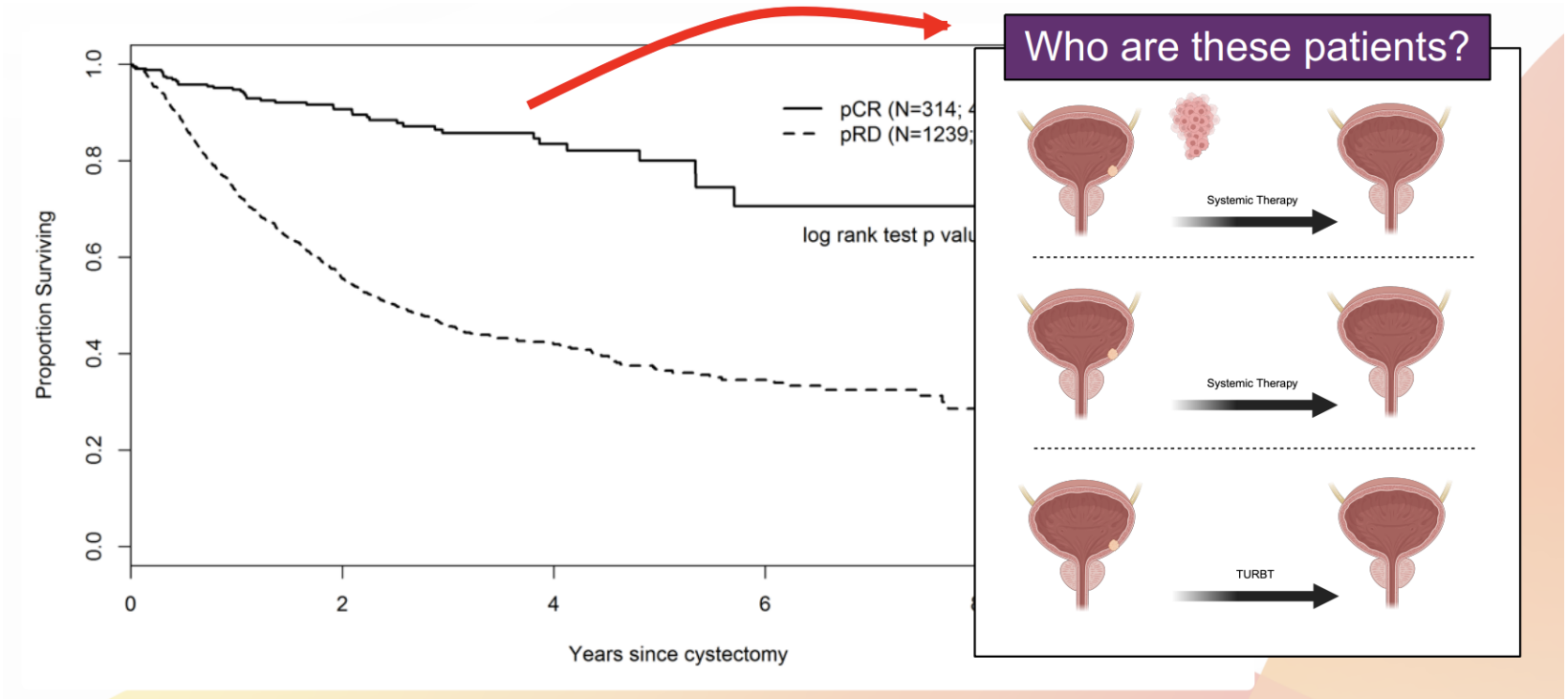
Grossmann HB et al. *N Engl J Med*. 2003;349(9):859–866.

	MVAC + Surgery	Surgery alone
5-yr survival	57%	43%

MVAC	All patients	cT2	cT3/4
ypT0	38% (48/126)	50% (26/52)	30% (22/74)



Grossman et al. N Engl J Med 2003

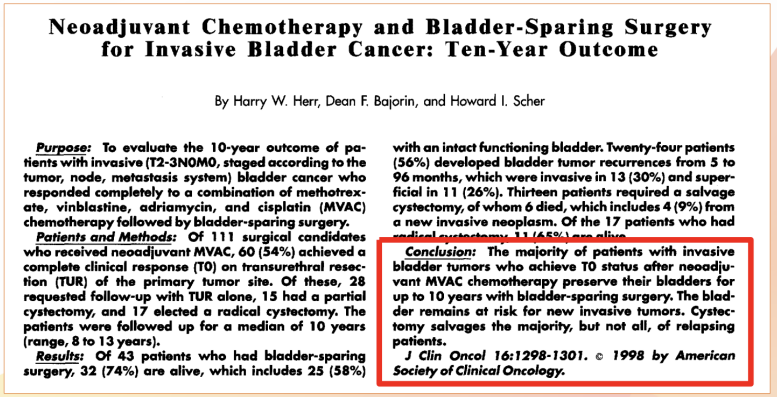


Courtesy of Dr. Galsky

TURBT AS MONOTHERAPY:

n: 151 MIBC

- 99 TURBT
- 52 RC



Neoadjuvant Chemotherapy and Bladder-Sparing Surgery for Invasive Bladder Cancer: Ten-Year Outcome

By Harry W. Herr, Dean F. Bajorin, and Howard I. Scher

Purpose: To evaluate the 10-year outcome of patients with invasive (T2-3N0M0, staged according to the tumor, node, metastasis system) bladder cancer who responded completely to a combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) chemotherapy followed by bladder-sparing surgery.

Patients and Methods: Of 111 surgical candidates who received neoadjuvant MVAC, 60 (54%) achieved a complete clinical response (T0) on transurethral resection (TUR) of the primary tumor site. Of these, 28 requested follow-up with TUR alone, 15 had a partial cystectomy, and 17 elected a radical cystectomy. The patients were followed up for a median of 10 years (range, 8 to 13 years).

Results: Of 43 patients who had bladder-sparing surgery, 32 (74%) are alive, which includes 25 (58%) with an intact functioning bladder. Twenty-four patients (56%) developed bladder tumor recurrences from 5 to 96 months, which were invasive in 13 (30%) and superficial in 11 (26%). Thirteen patients required a salvage cystectomy, of whom 6 died, which includes 4 (9%) from a new invasive neoplasm. Of the 17 patients who had

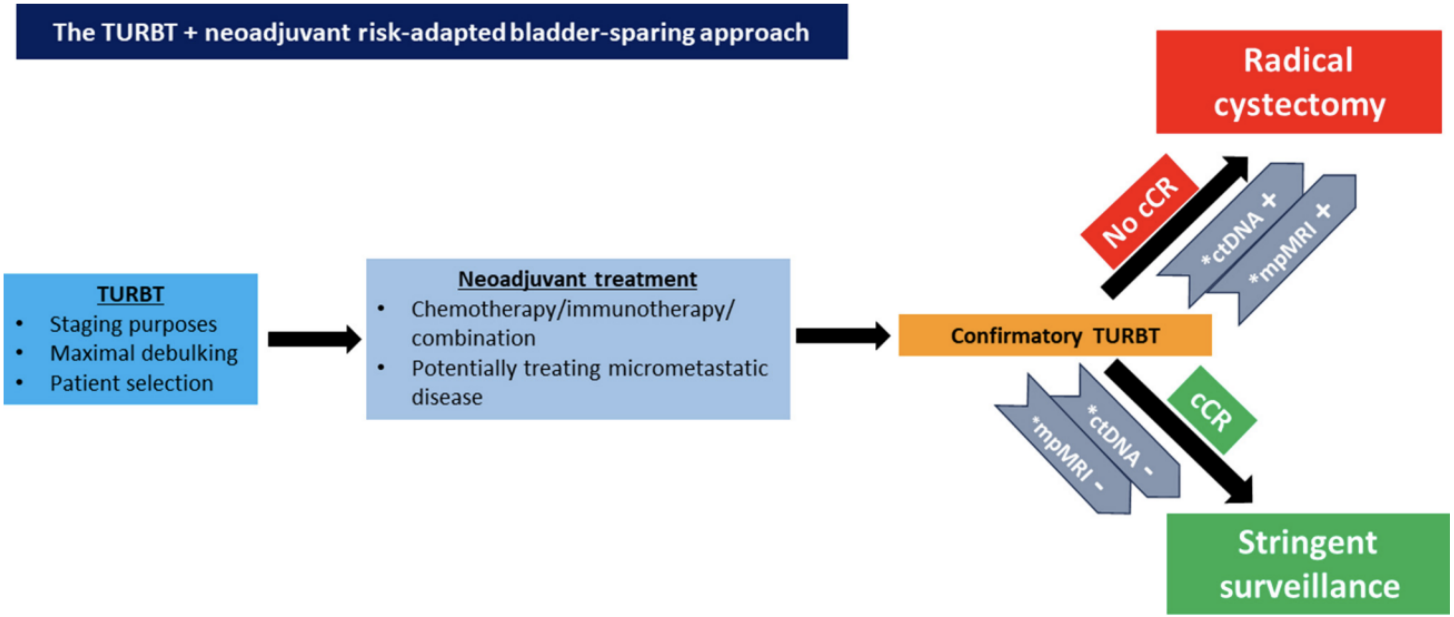
Conclusion: The majority of patients with invasive bladder tumors who achieve T0 status after neoadjuvant MVAC chemotherapy preserve their bladders for up to 10 years with bladder-sparing surgery. The bladder remains at risk for new invasive tumors. Cystectomy salvages the majority, but not all, of relapsing patients.

J Clin Oncol 16:1298-1301. © 1998 by American Society of Clinical Oncology.

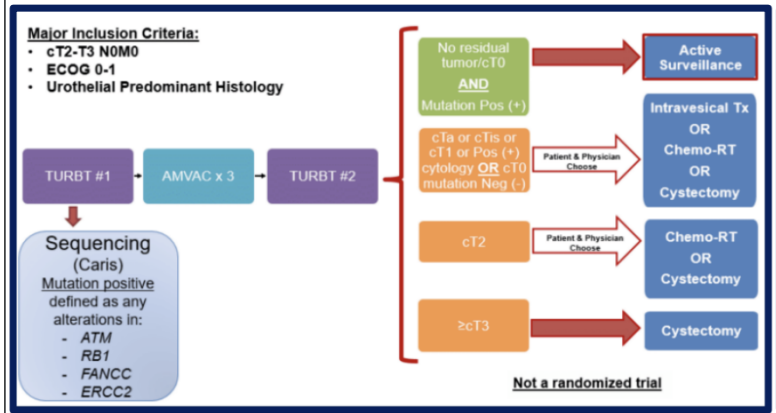
10-year disease-specific survival:	• 76% TURBT (57% bladder preserved) • 71% RC (P = 0.3)
99 TURBT, 10y survival:	• cT0: 82% • cT1: 57% (P = 0.003)
Relapse after TURBT (34%)	• 53% late RC • 16% death

Herr, JCO 2001

PERSONALISED RISK-ADAPTED BLADDER SPARING APPROACH USING TURBT + NEOADJUVANT THERAPY

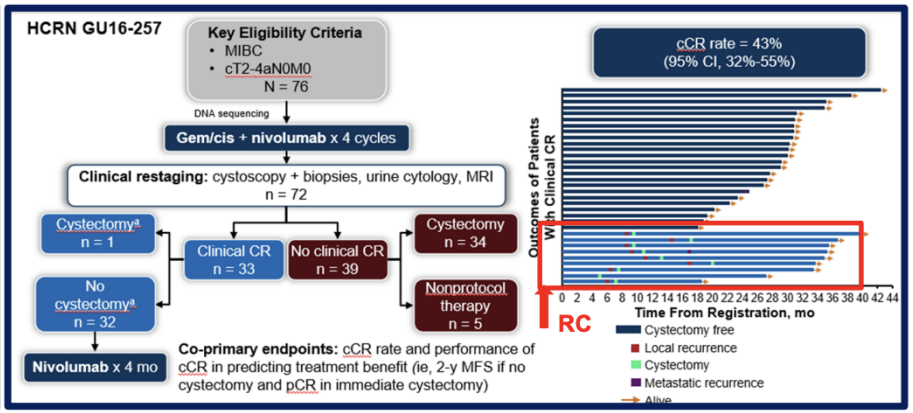


B-D Reuben, Trends in Molecular Medicine 2024

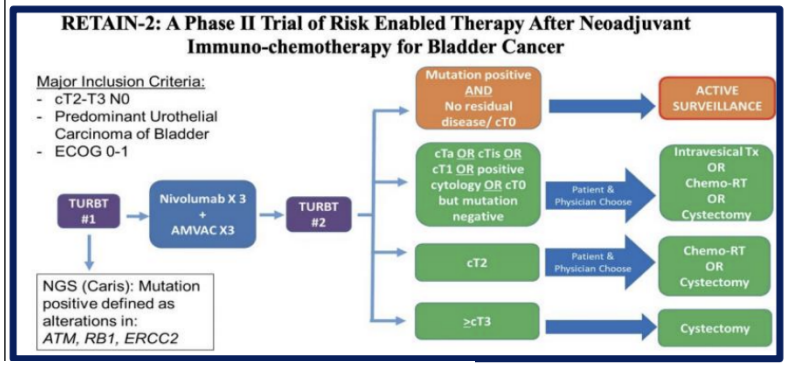


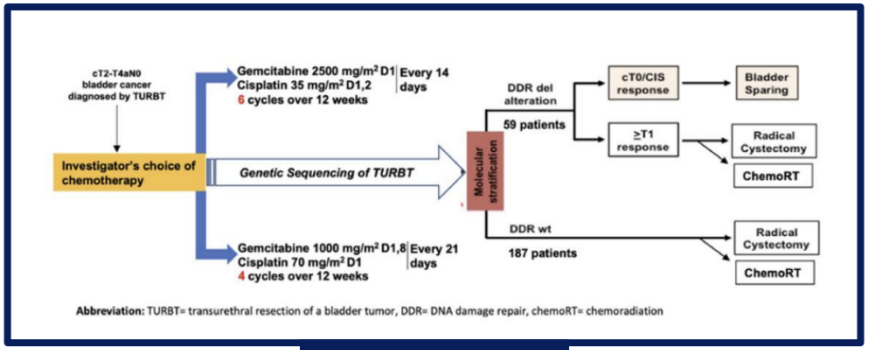
RETAIN Trial did not meet 2 year MFS endpoint

Geynisman D et al. ASCOGU23



Galsky MD et al. Nature 2023



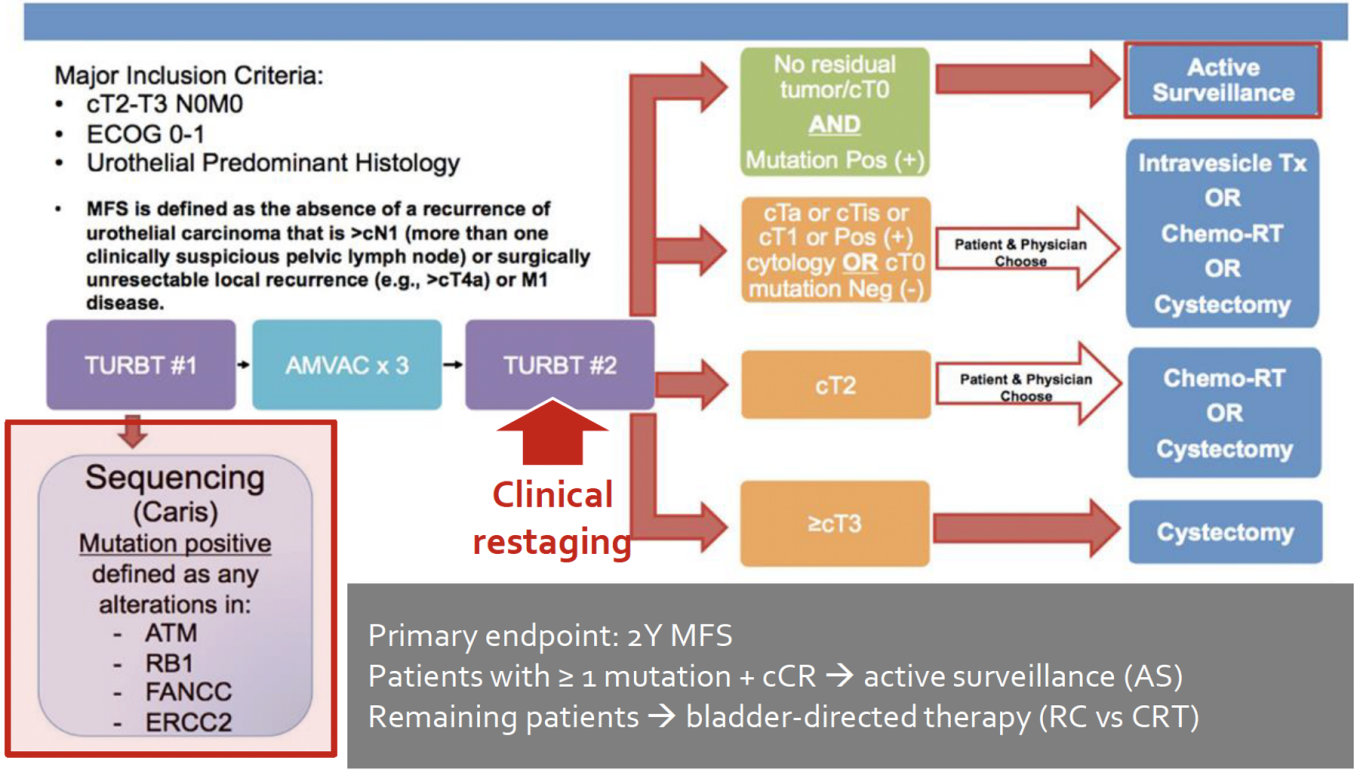


A031701

CRITICAL CHALLENGES OF BLADDER PRESERVATION (BP)

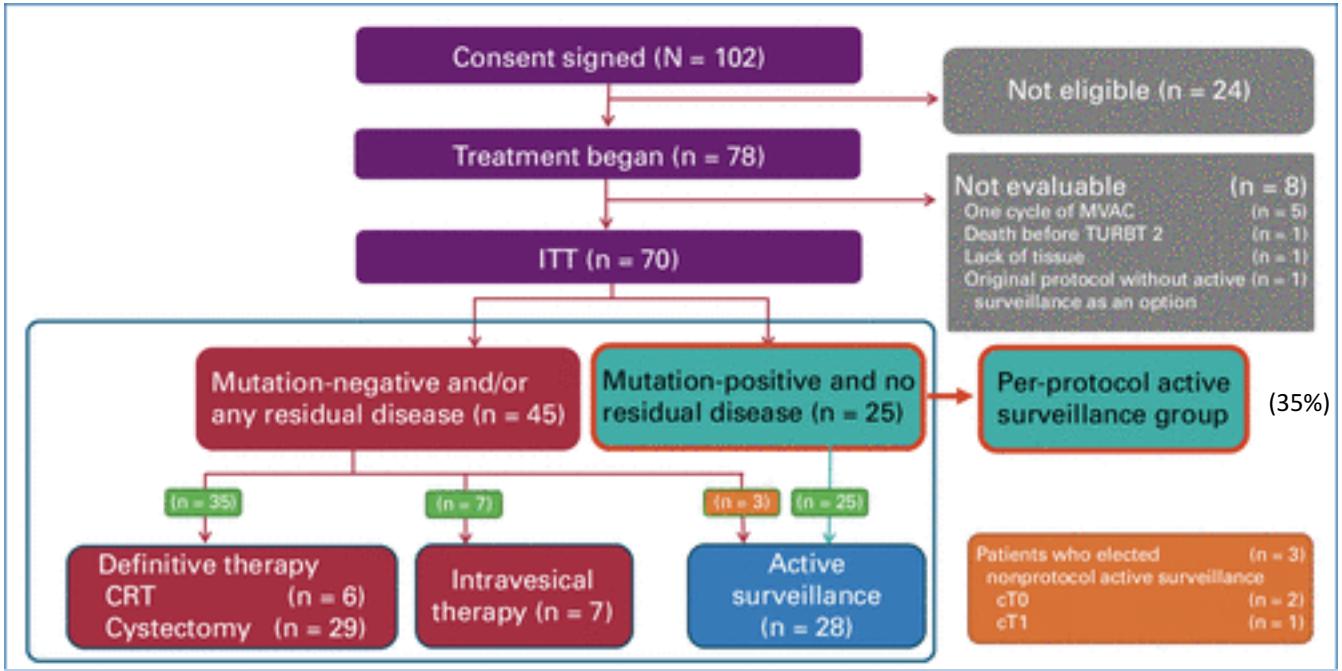
2. **Could we better select patients for BP?**
   - Predictive and prognostic biomarkers

RETAIN-1 TRIAL: Using DNA Damage Repair mutations to guide Bladder cancer treatment



Geynisman ASCO GU 2023, Geynisman JCO 2024

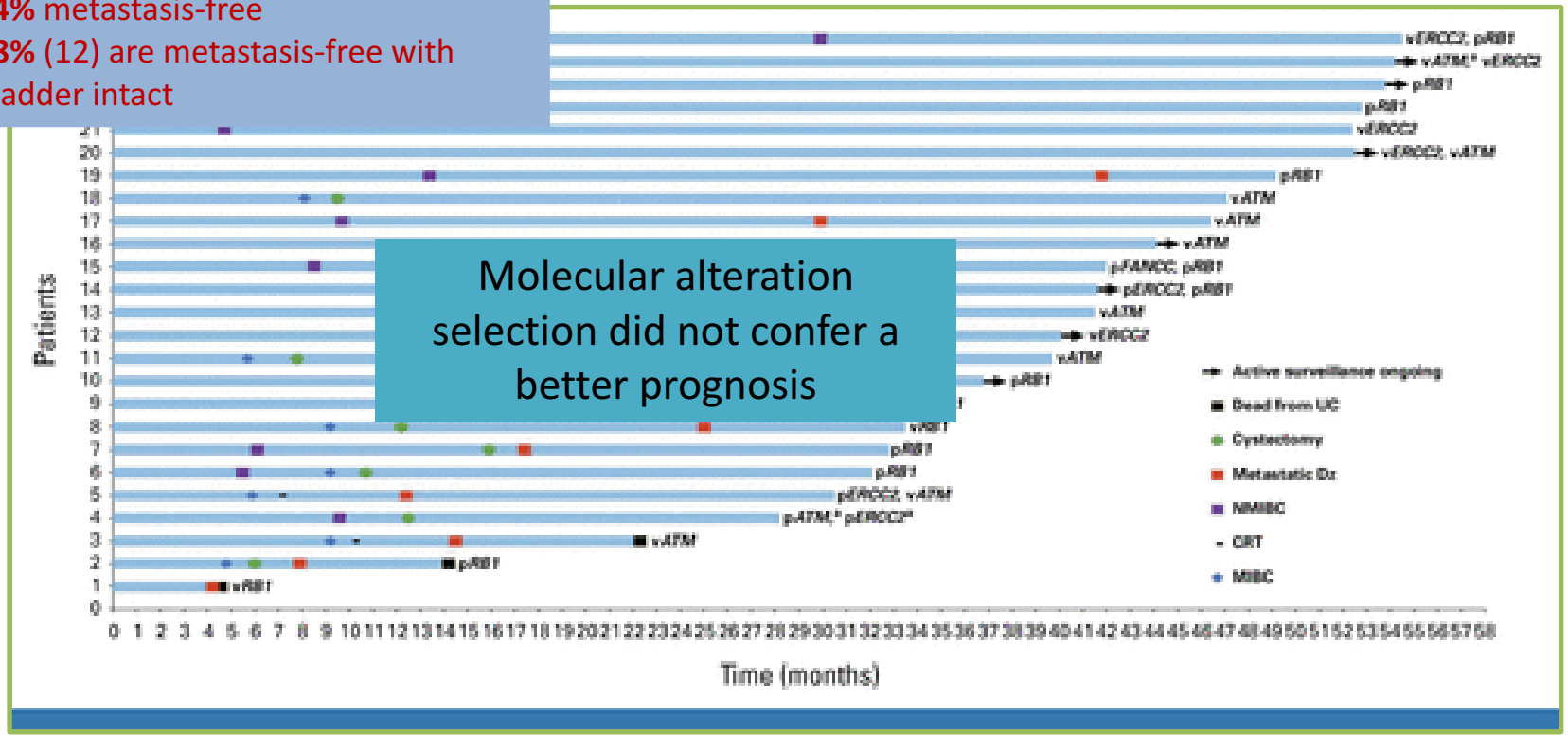
RETAIN-1 TRIAL: Using DNA Damage Repair mutations to guide Bladder cancer treatment



2-year MFS for the ITT patients was 72.9%

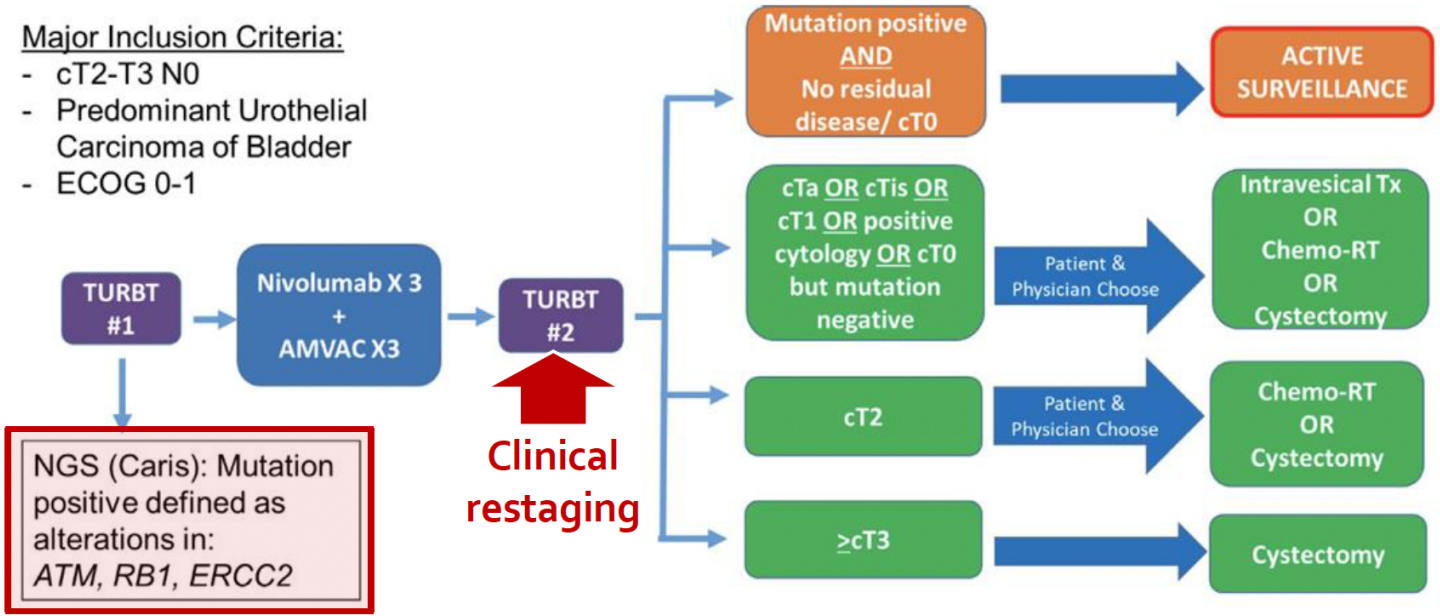
Geynisman JCO 2024

- **68%** (17)had UC recurrence
  - 8 underwent RC (7 for MIBC,4 N+)
- **36%** (9) developed metastasis
  - 8 recurred in bladder first
- **64%** metastasis-free
- **48%** (12) are metastasis-free with bladder intact



Geynisman JCO 2024

RETAIN-2 TRIAL:

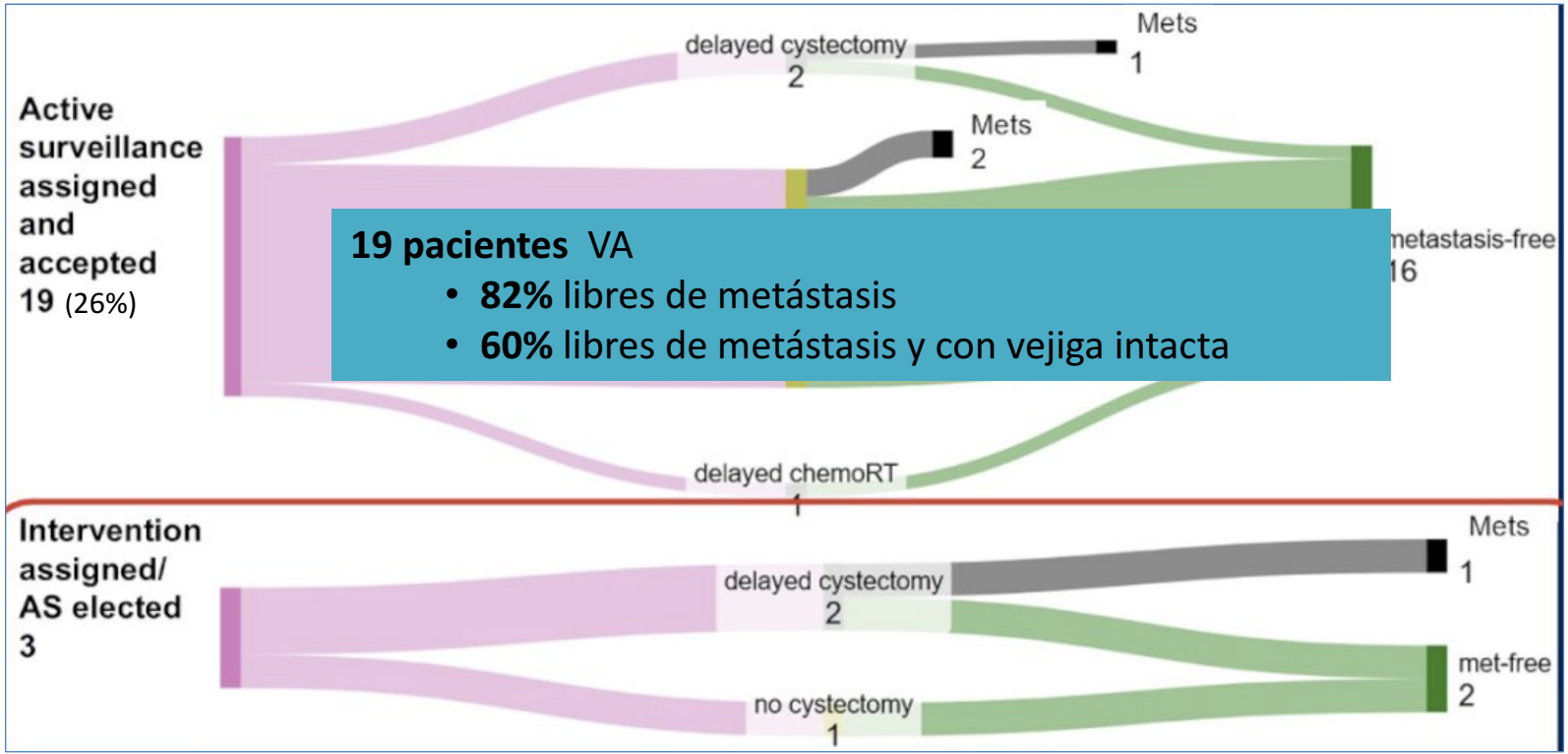


Metastasis-free survival (MFS) is defined as the absence of a recurrence of urothelial carcinoma that is >cN1 (more than one clinically suspicious pelvic lymph node) or surgically unresectable local recurrence (e.g., >cT4a) or M1 disease).

Primary endpt:
2-yr Metastasis-free survival
Follow-up: 5 years

Ghatalia P, ASCO GU 2025

RETAIN-2 (n=71) (mFU 21.7M)

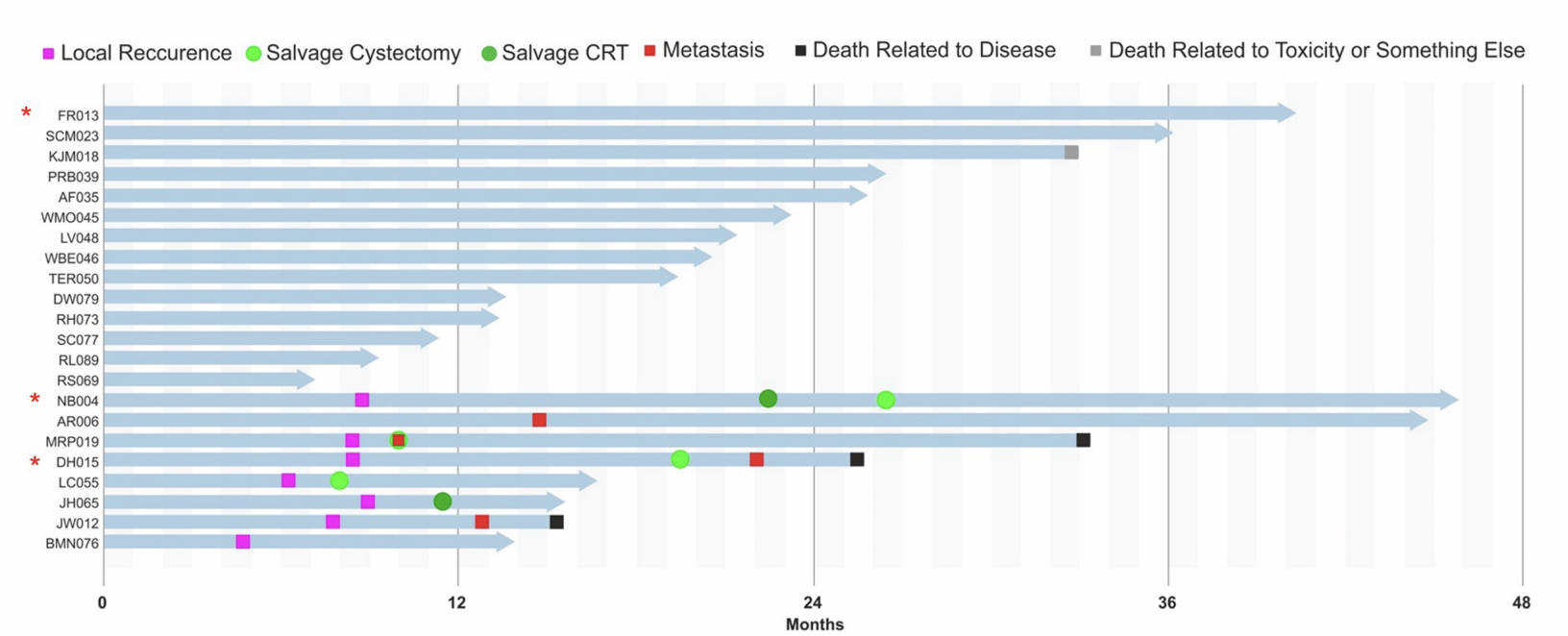


19 pacientes VA

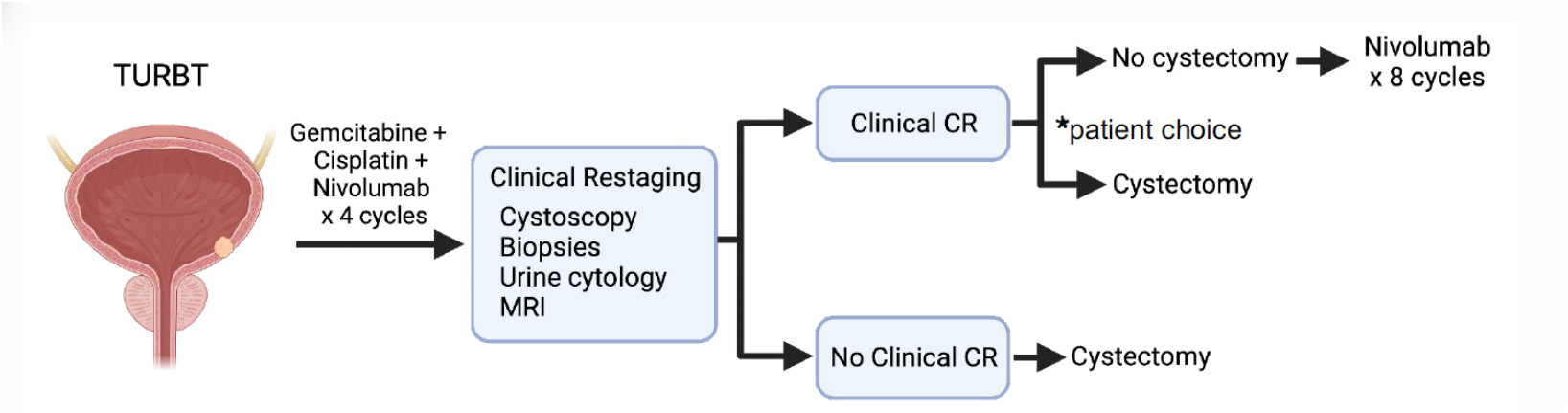
- **82%** libres de metástasis
- **60%** libres de metástasis y con vejiga intacta

Ghatalia P, ASCO GU 2025

OUTCOMES OF 22 PATIENTS ON ACTIVE SURVEILLANCE (mFU 21.7 mo)



HCRN GU 16-257: Response-guided bladder sparing

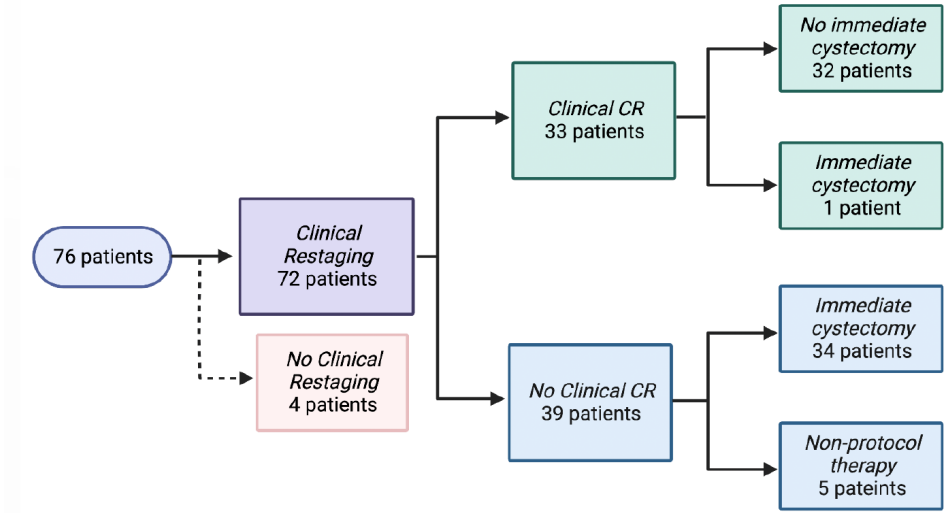


Co-primary endpoints

- 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 et al, Nature Medicine 2023

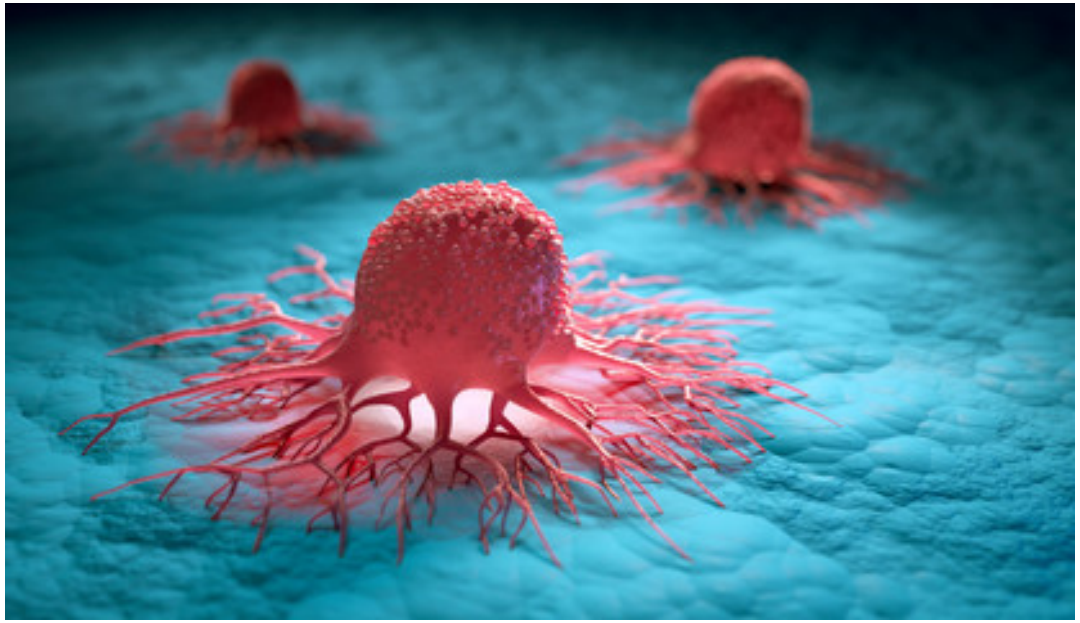
HCRN GU 16-257: Response-guided bladder sparing



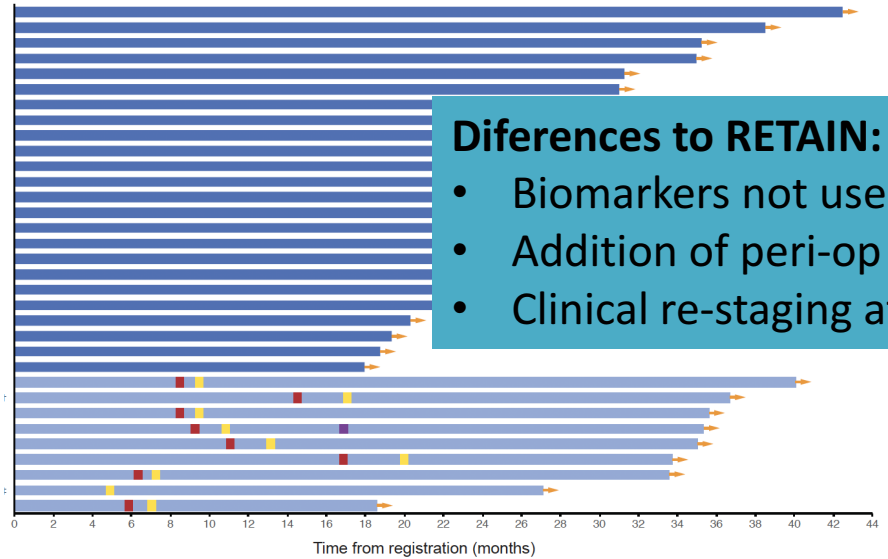
Clinical CR rate = 43% (95% CI: 32%, 55%)

Galsky et al, Nature Medicine 2023

Are these remisions going to be durable?

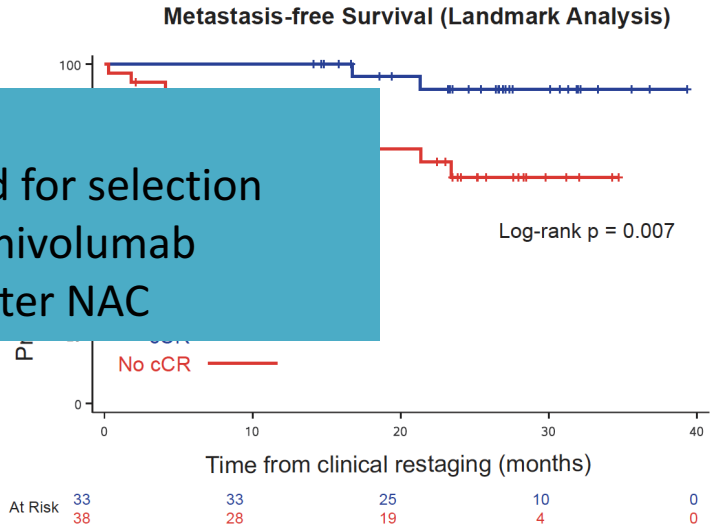


HCRN GU 16-257: Clinical Outcomes



Diferences to RETAIN:

- Biomarkers not used for selection
- Addition of peri-op nivolumab
- Clinical re-staging after NAC



Galsky et al Nature Medicine 2023

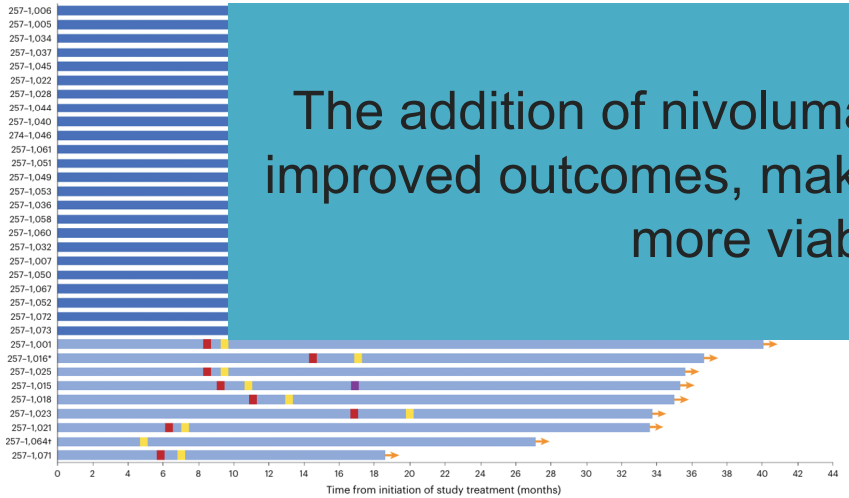
Positive predictive value of clinical CR for 2 year MFS:
0.97 (95% CI: 0.91, 1)

Role of “delayed” cystectomy in patients with local recurrence?

Bladder Preservation Strategies

HCRN GU 16-257: GemCis + Nivo + Selective BP

Clinical outcomes of achieving a cCR (33) – cCR rate 43% (95% CI 32-55%)

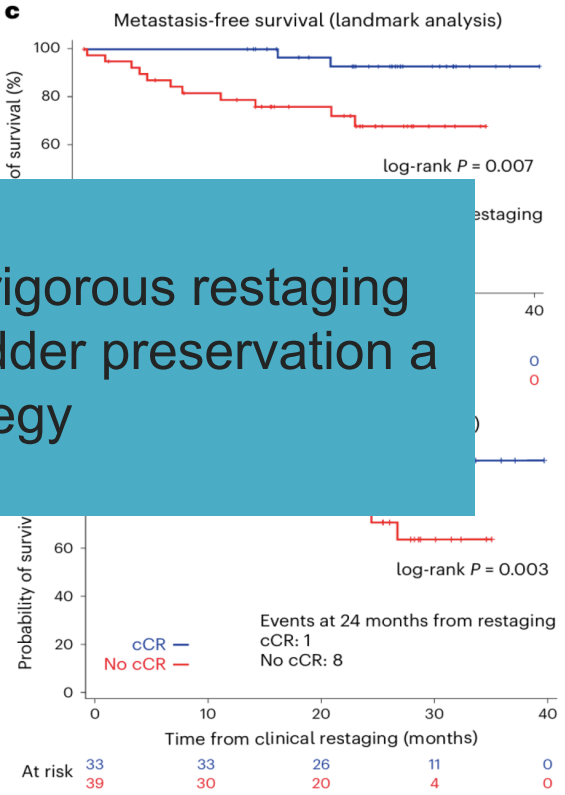


cCR rates higher in ERCC2 mutations or TMB ≥10 mut/Mb (NSS)

Somatic alterations in pre-specified genes (ATM, RB1, FANCC and ERCC2)

- Did not improve the positive predictive value of cCR

The addition of nivolumab and rigorous restaging improved outcomes, making bladder preservation a more viable strategy



Galsky et al, Nature Medicine 2023

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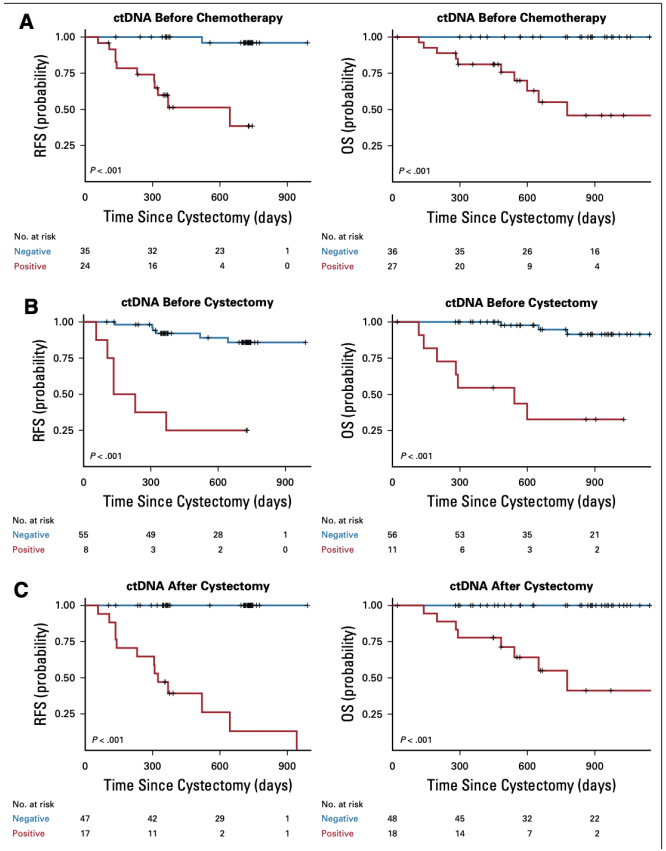
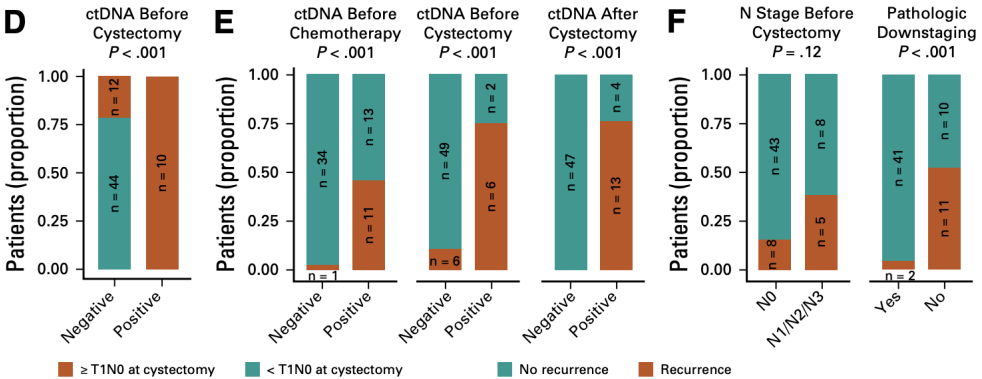


Early Detection of Metastatic Relapse and Monitoring of Therapeutic Efficacy by Ultra-Deep Sequencing of Plasma Cell-Free DNA in Patients With Urothelial Bladder Carcinoma

Emil Christensen, PhD[1]; Karin Birkenkamp-Demtröder, PhD[1]; Himanshu Sethi, MPH[2]; Svetlana Shchegrova, PhD[2]; Raheleh Salari, PhD[2];

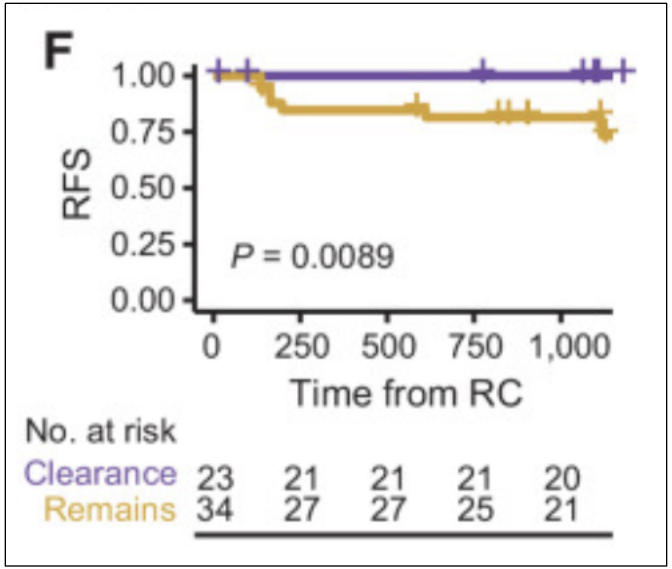


Christensen E, JCO 2019

Clin Cancer Res. 2023 Feb 13;29(8):1582–1591. doi: 10.1158/1078-0432.CCR-22-3250

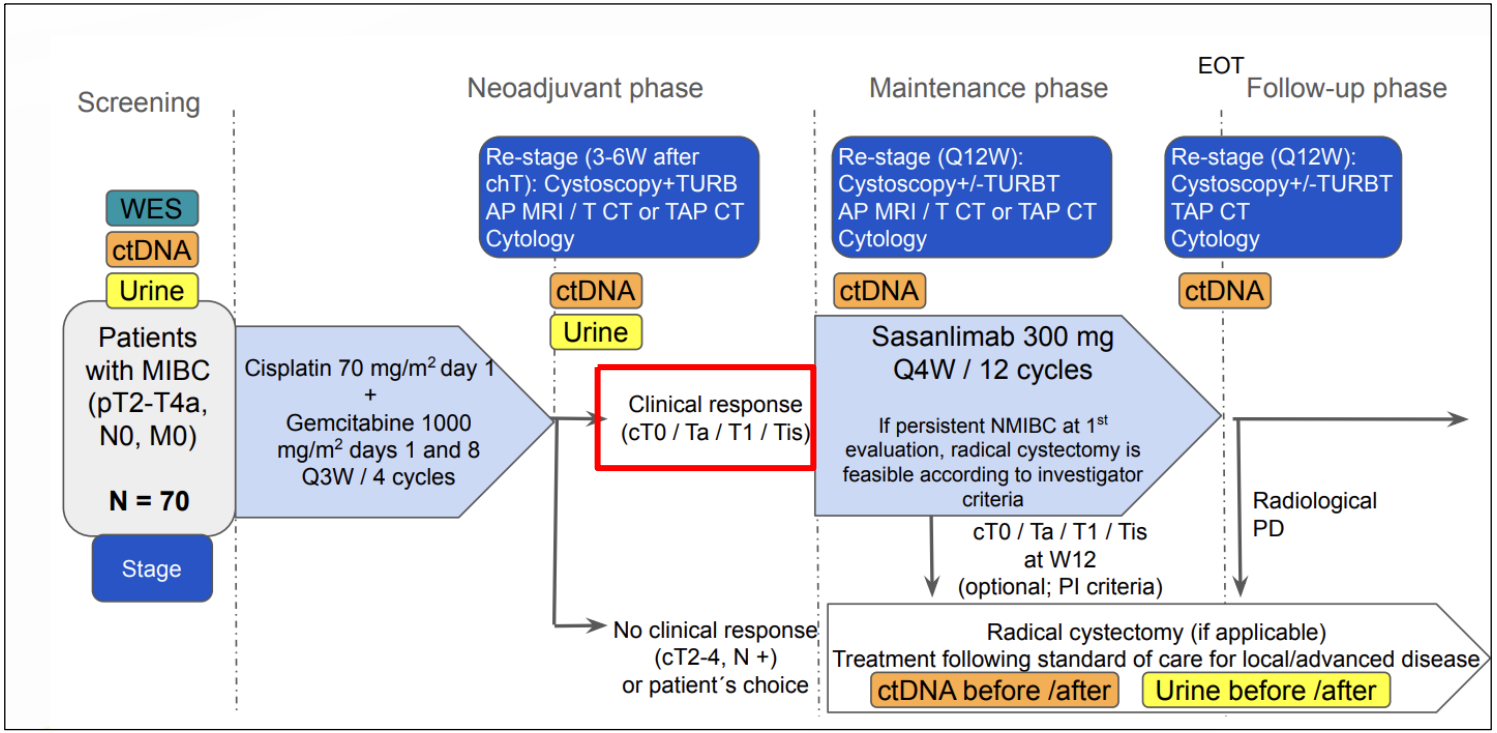
Cell-Free Urine and Plasma DNA Mutational Analysis Predicts Neoadjuvant Chemotherapy Response and Outcome in Patients with Muscle-Invasive Bladder Cancer

Emil Christensen [1,2,#], Iver Nordentoft [1,#], Karin Birkenkamp-Demtröder [1,2], Sara K Elbæk [2], Sia V Lindskrog [1,2],



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

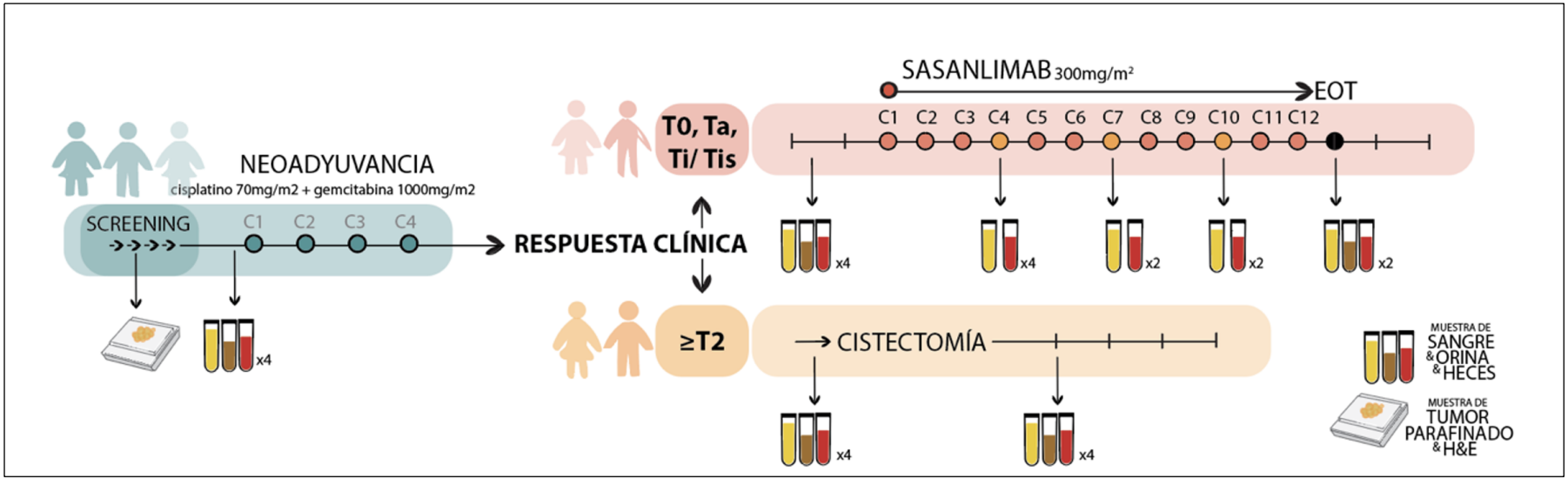
SASAN-SPARING: Sasanlimab as bladder-sparing maintenance treatment after neoadjuvant chemotherapy in patients with MIBC



Sevillano E and De Velasco G

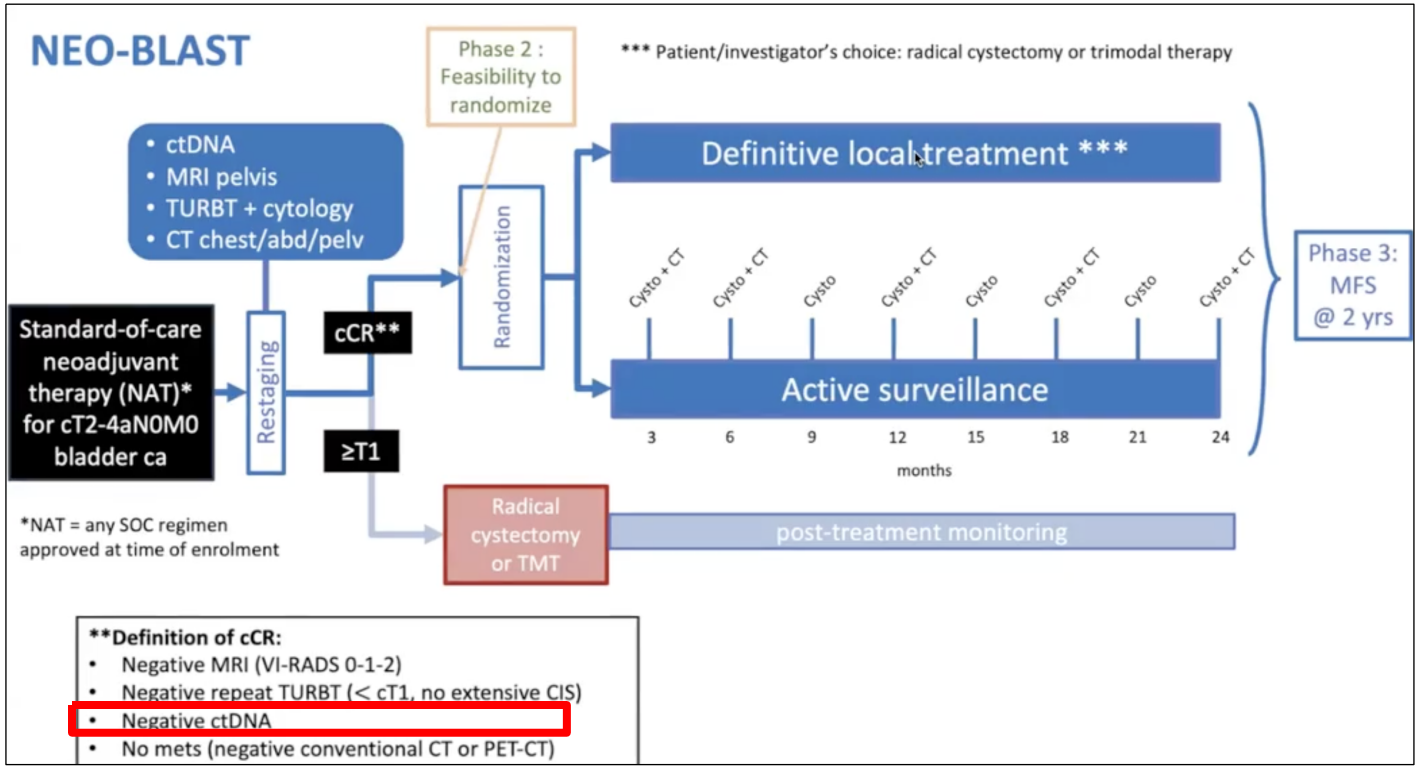
SASAN-SPARING: ctDNA, utDNA ,microbiome profiling

WE ARE RECRUITING !



Sevillano E and De Velasco G

NEO-BLAST:

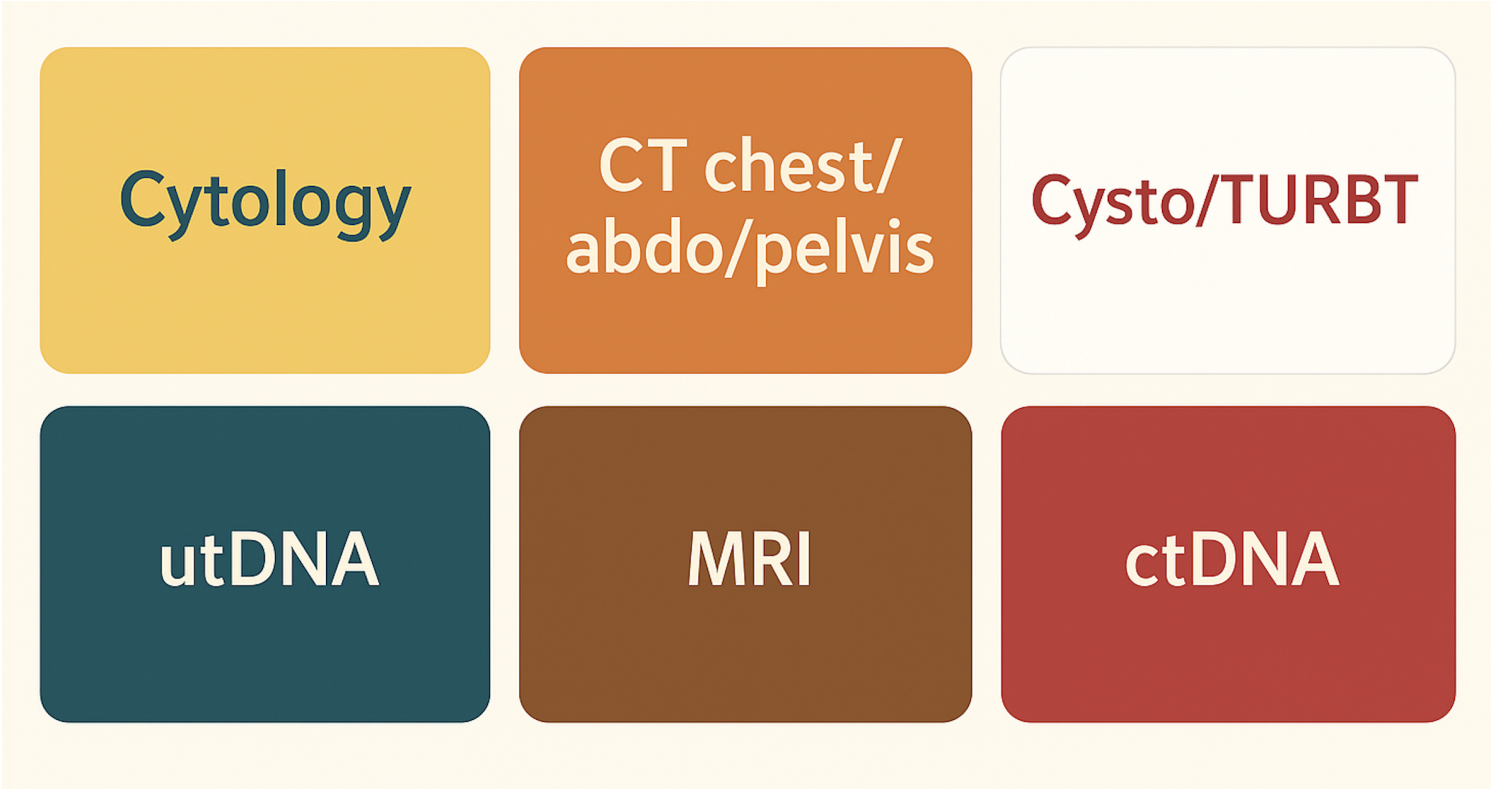


Marie-Pier St-Laurent, AUA 2025

CRITICAL CHALLENGES OF BLADDER PRESERVATION (BP)

3. Do we have rigorous methods to measure and define clinical complete response?

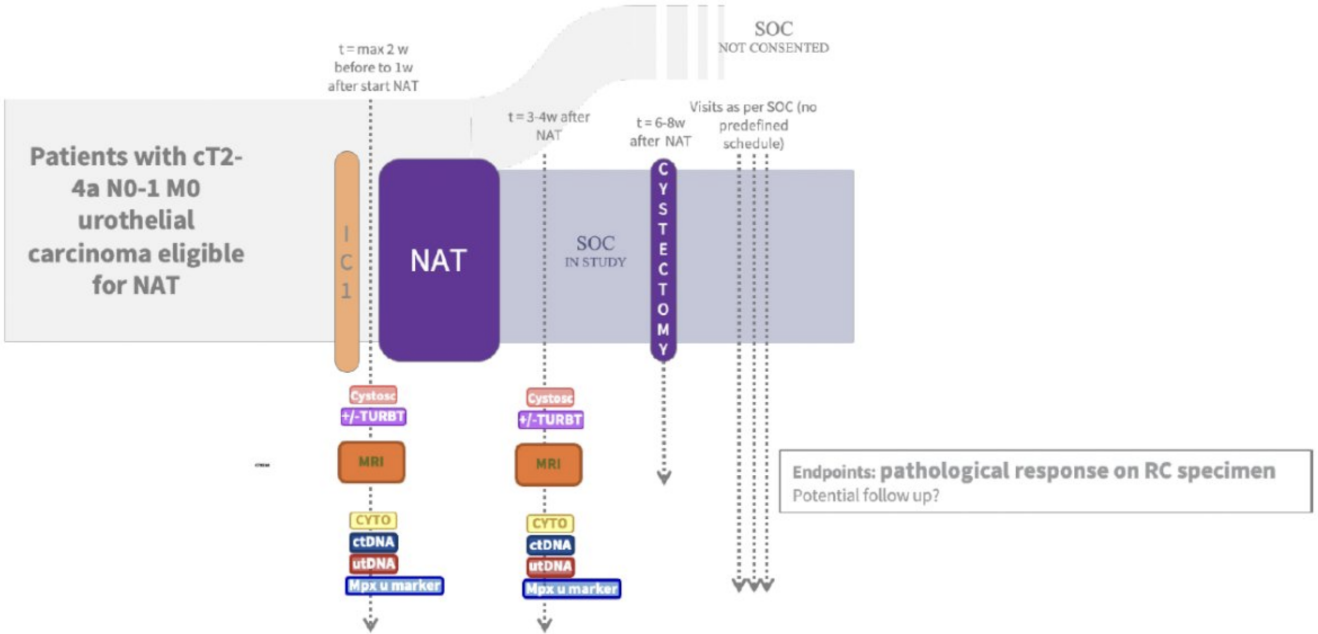
DETERMINING COMPLETE RESPONSE



cCR AND pCR CORRELATION?

> Eur Urol Oncol. 2025 Apr 15:S2588-9311(25)00080-X. doi: 10.1016/j.euo.2025.03.005.
Online ahead of print.

Challenges in Defining Clinical Complete Response to Systemic Therapy in Muscle-invasive Bladder



Masson-Lecomte, Eur Urol Onc 2025

CRITICAL CHALLENGES OF BLADDER PRESERVATION (BP)

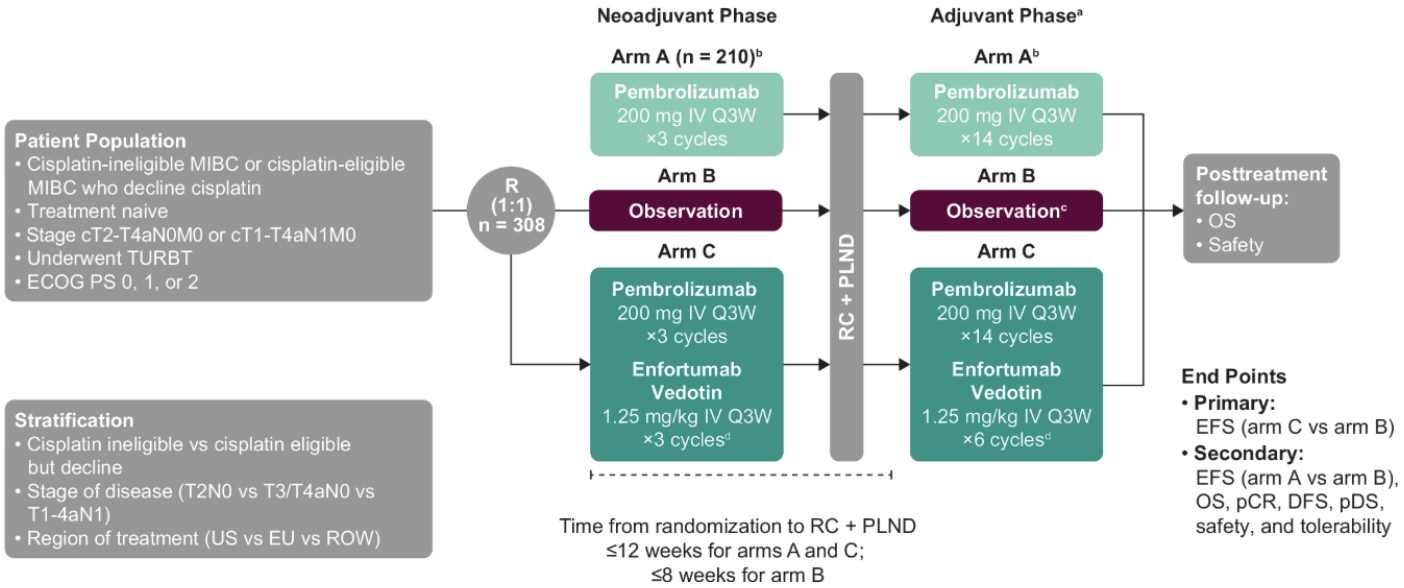
4. Can more efective systemic therapy increase BP rates?

- IO, ADC

KEYNOTE-905/EV-303: ESMO 2025 AWAITED RESULTS!

Methods

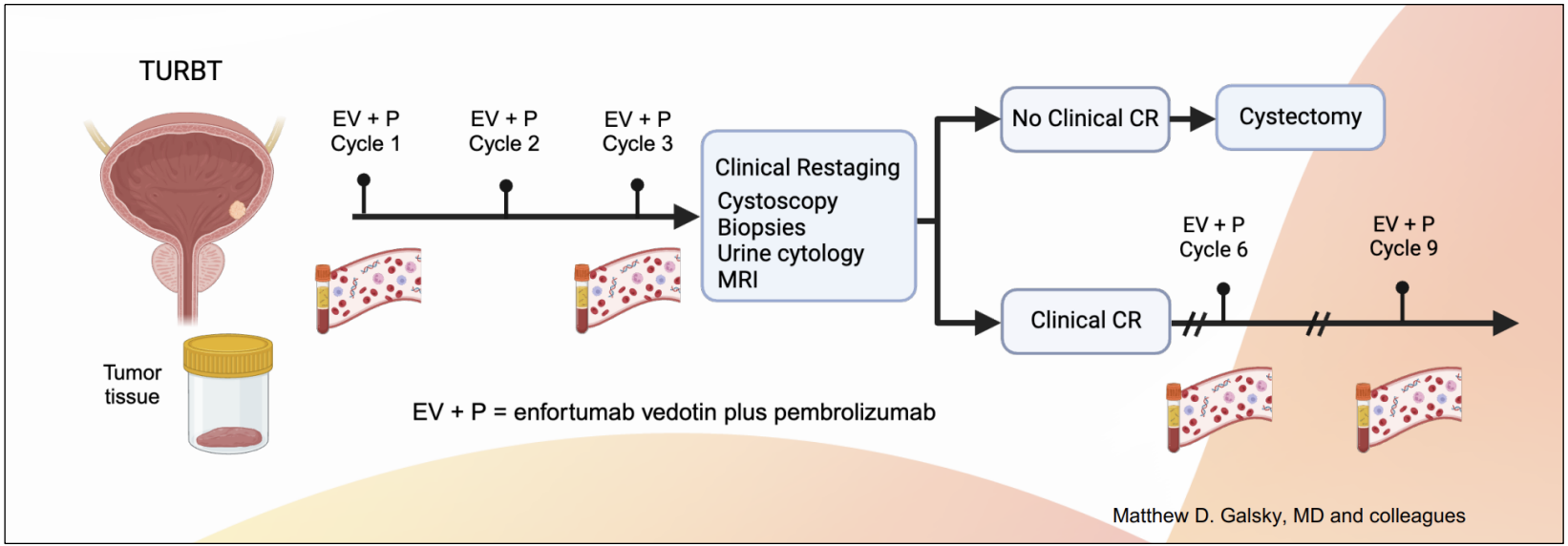
Study design



THE MORE pCR, THE MORE REASONS TO PRESERV BLADDERS?

Vulsteke C, ESMO 2025

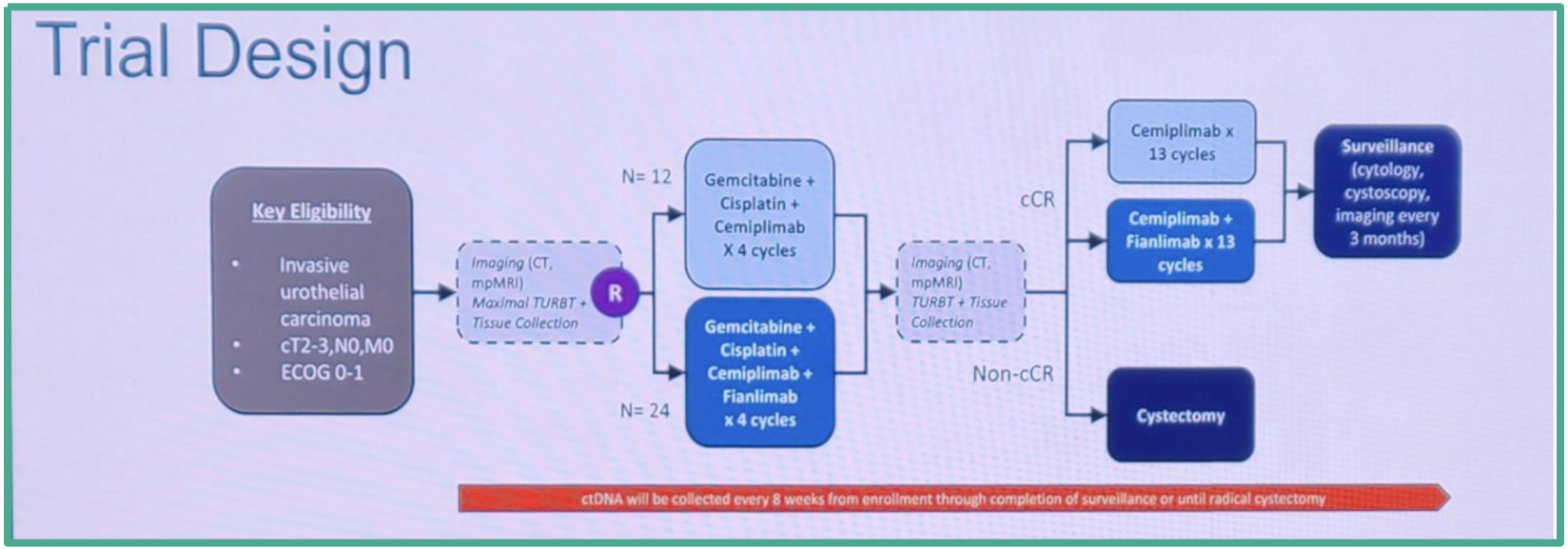
HCRN GU22-598: Response-guided bladder sparing with EV + pembrolizumab (NCT06809140)



Galsky M

NeoSTOP-IT:

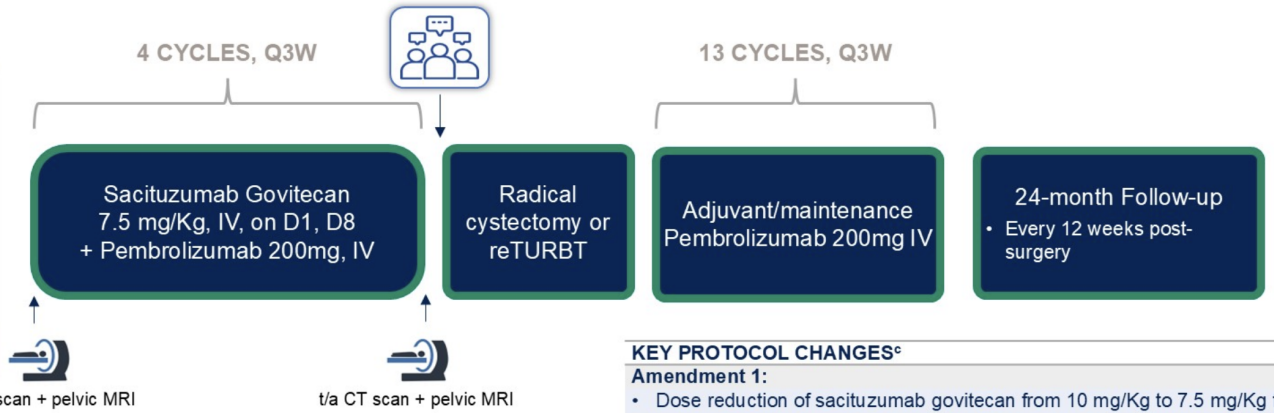
A Phase 2, Randomized, Open-Label Study of Gemcitabine/Cisplatin plus Cemiplimab (REGN2810, Anti-PD-1) with or Without Fianlimab (REGN3767, Anti-LAG-3) for Organ Preservation in MIBC



SURE-02

NCT05535218

Population:
- Aged ≥18 years
- Histologically confirmed cT2-T3b N0M0 MIBC (absence of nodal or metastatic disease at screening)
- Predominant UC histology
- ECOG PS of 0-1
- Ineligible or refusing NAC
- Ineligible or refusing chemoRT
- Scheduled for RC



Primary endpoint:
- Clinical CR rate (imaging CR + ypT0Nx)

Secondary endpoints:
- Efficacy: any downstaging rate, EFS[a], MFS, BI-EFS[b], OS, after neoadjuvant treatment
- Safety (CTCAE v.5.0)

Exploratory endpoints
- Biomarkers of response
- Changes in biomarker expression
- Microbiome data in urine and feces

KEY PROTOCOL CHANGES[c]

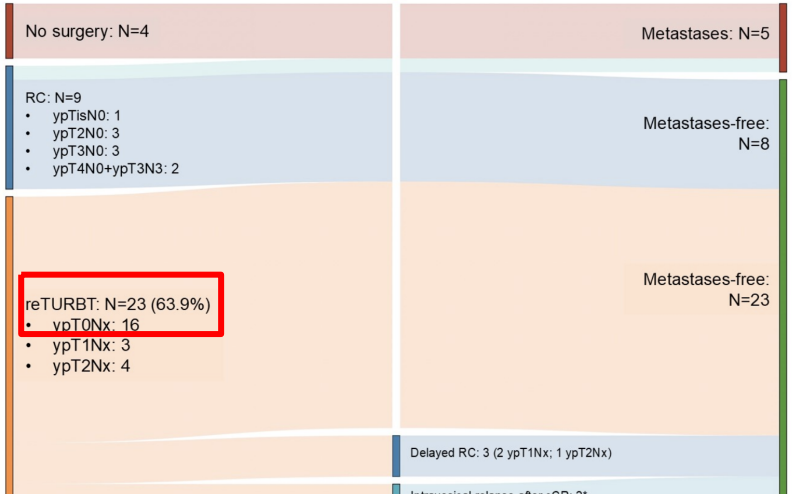
Amendment 1:
- Dose reduction of sacituzumab govitecan from 10 mg/Kg to 7.5 mg/Kg from C1D1.
- Introduction of G-CSF use (Peg-GCSF) as primary prophylaxis since C1D9.
- Exclusion of patients who had ≥3 risk factors for febrile neutropenia as indicated by the ASCO guidelines.[d]

Amendment 2:
- Change in primary endpoint from ypT0N0 rate to cCR rate (no change in sample size and statistical plan)
- Addition of a further inclusion criterion:
  - ChemoRT refusing/unsuited patients
- Restriction to cT2-T3bN0M0 patients.

Necci A, ASCO 2025

Interim Results of SGP: Clinical and Pathological Responses

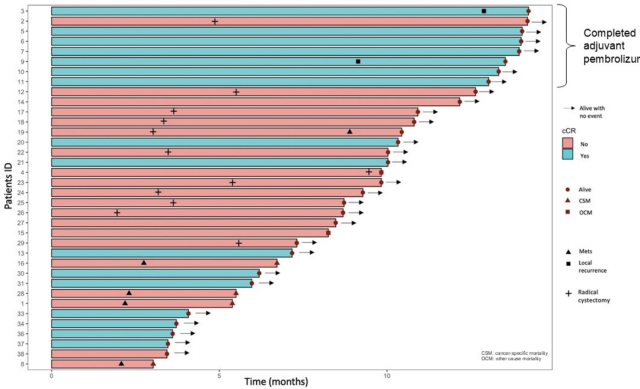
PD post-neoadjuvant SGP: N=4 (11.1%)

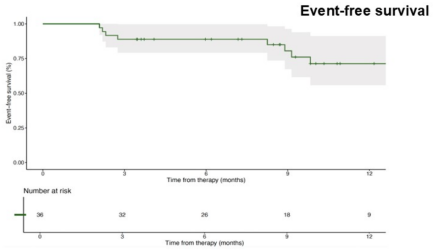


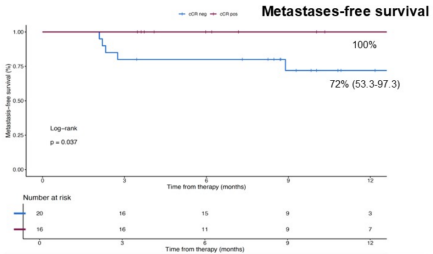
ITT Population (N=36):

- **cCR: 16 (44.4%; 95%CI: 27.9–61.9)**
- ypT≤1N0-x: 20 (55.6%)

Median Follow-up: 10 months (IQR: 7.3 – 13)

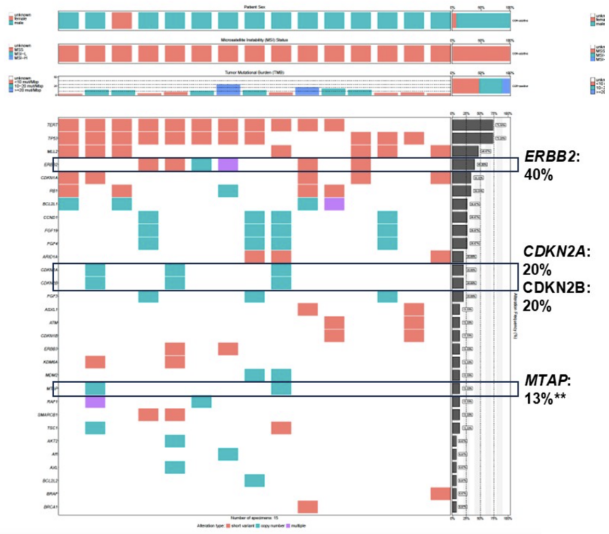






- 12m EFS:[a] 71.3% (95%CI: 55.7-91.2)
- 12m MFS: 84.2% (95%CI: 72-98.5)
- 12m Bladder-intact-EFS[b] in cCR patients (N=16): 100%
- 12m Bladder-intact-EFS in reTURBT patients (N=23): 74% (95%CI 54.8-99)

cCR (N=15)



QUESTIONS TO BE ANSWERED:

Reliable CR assessment → exclude residual disease

Salvage strategies → essential for recurrence/progression

Intravesical recurrences → key management in preservation

Imaging → mpMRI (local staging), FDG-PET/CT (nodal disease, ↓ understaging)

Biomarkers → ctDNA for selection, scheduling, multimodal therapy

Limitations → variant histologies, incomplete NAC → need for cystectomy

KEY TAKE AWAY FOR BLADDER SPARING: