

Bladder cancer session

Avoiding local treatment: is this the ultimate goal?

Contra

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Meeting on Urological Cancers**

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Conflicts of interest

- I have the following potential conflict(s) of interest to report

Speaker for a pharmaceutical company: BMS, MSD, Johnson&Johnson, Astellas, Astra zeneca

Support from a pharmaceutical company for participation in a national or international congress: Bouchara Recordati, BMS, MSD, Johnson&Johnson, Ipsen, Astellas, Photocure, Astra zeneca

Consultant : Johnson&Johnson, BMS, MSD, Photocure, Karl Storz, Merck Serono

Principal investigator of a pharmaceutical industry trial: MSD, Johnson&Johnson, Fidia, Steba Biotech, Astra zeneca, Astellas

Shares in a pharmaceutical laboratory: None

MAIN Conflict of Interest Disclosure

**Research interest in bladder
preservation for MIBC
(RT-based therapy)**



Avoiding local treatment – Facts

- Just because something is attractive DOES NOT mean we have the evidence to do it !
- **The idea is attractive**
 - Maximal TURBT + systemic therapy alone can achieve pCR
 - Many patients would love the idea to keep their bladder
 - New regimens are pushing pT0 rate very high
- **YES, but :**
 - cCR definition is NOT perfect
 - Bladder preservation dataset does have caveats
 - How long a cCR can be maintained?

Let's go back a few years...

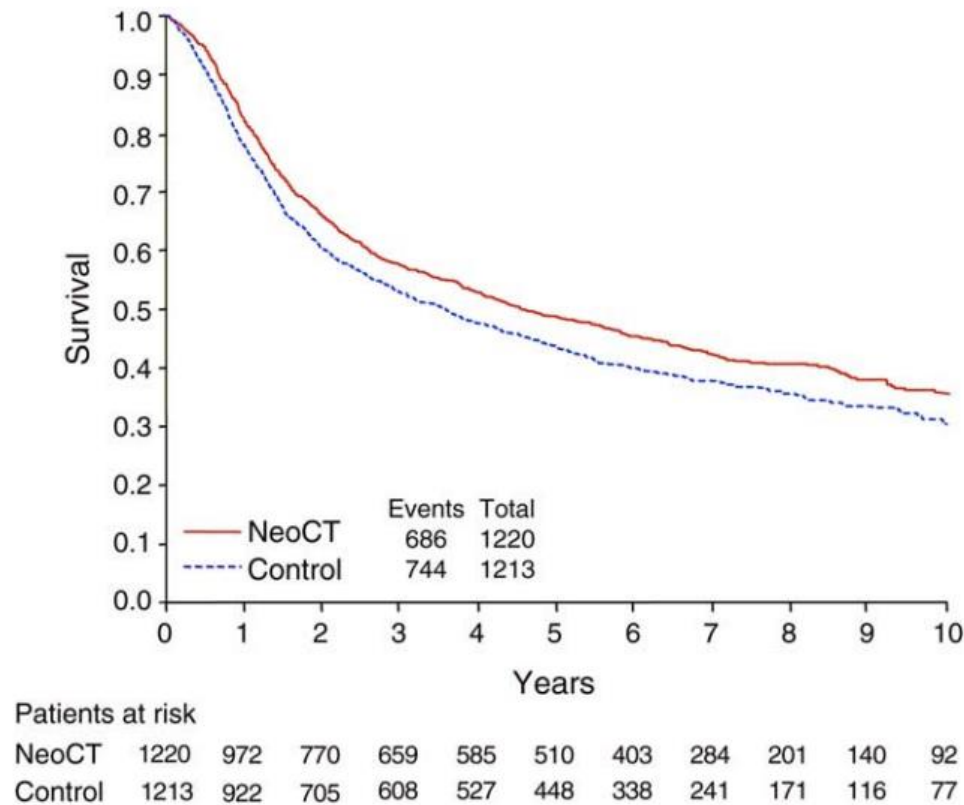


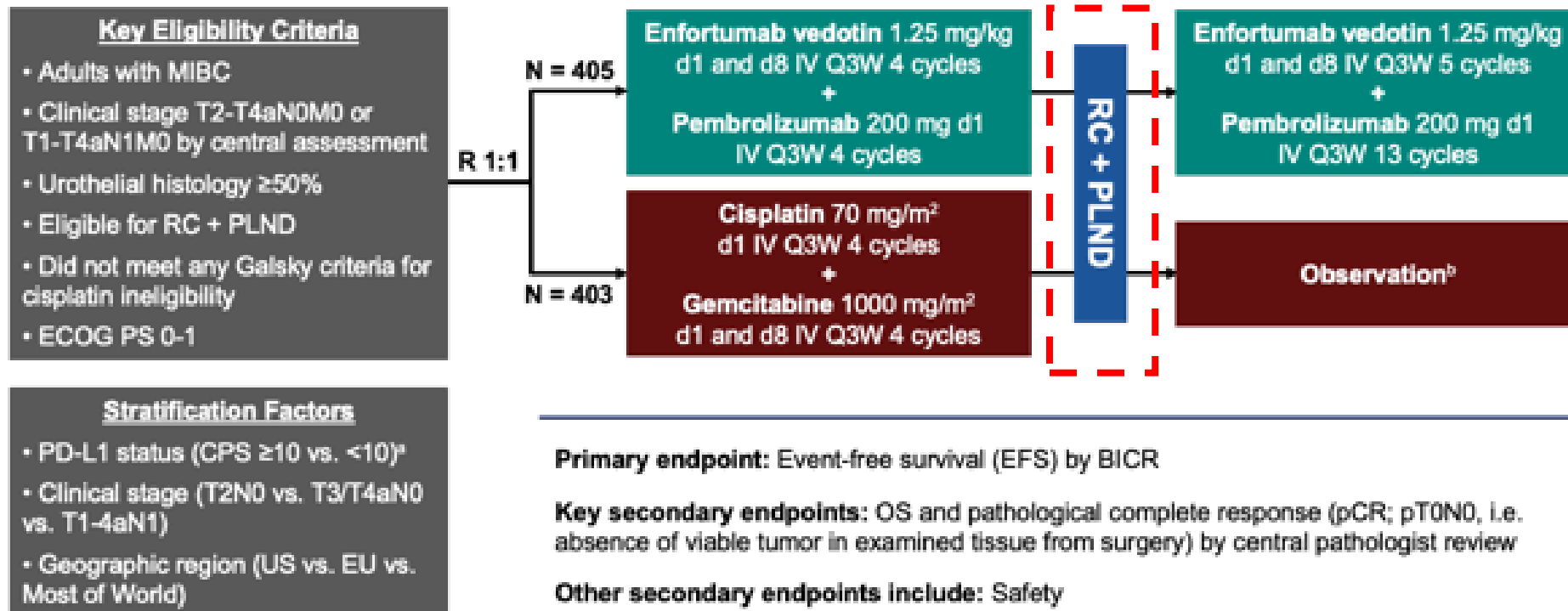
Fig. 2. Overall survival curve (platinum based combination chemotherapy trials only).

- 5% absolute OS at 5 years
- 9% DFS at 5 years

➔ Physical bladder treatment was mandatory !

RC IS STILL PART OF THE PLAN !

KEYNOTE-B15/EV-304 Study (NCT04700124)



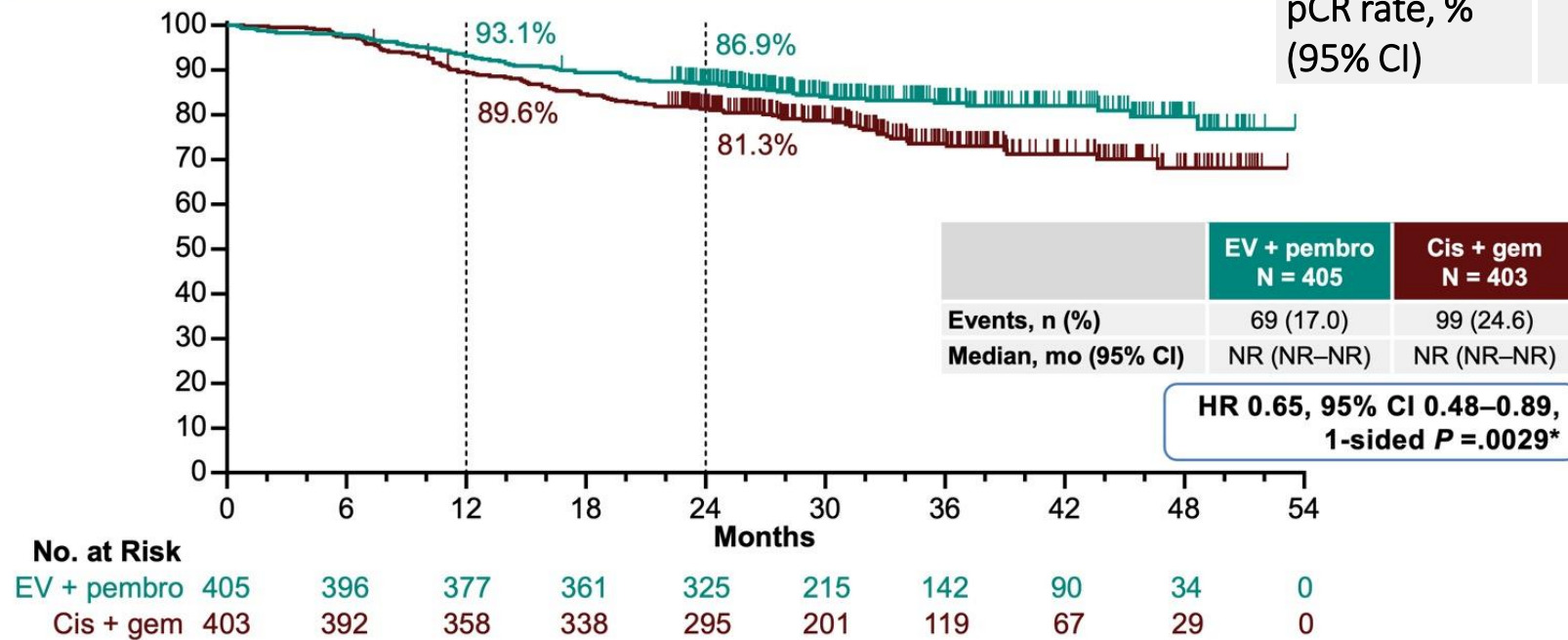
BICR, blinded independent central review; CPS, combined positive score; IV, intravenous; Q3W, every 3 weeks.

^aAssessed by PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA); CPS = # PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) + total # viable tumor cells × 100.

^bAs of Feb 2023, adjuvant nivolumab was permitted when clinically indicated and regionally available.

Data cutoff date: 27 October 2025

Key Secondary Endpoint: OS ITT Population



- In total, 44/87 (50.6%) of pts with an EFS event in the EV + pembro arm and 86/146 (58.9%) of pts with an EFS event in the cis + gem arm received any subsequent systemic therapy

NR, not reached. * denotes statistical significance (one-sided boundary 0.0038).

Data cutoff date: 27 October 2025

EV 304/ KN B15 + ABC meta analysis

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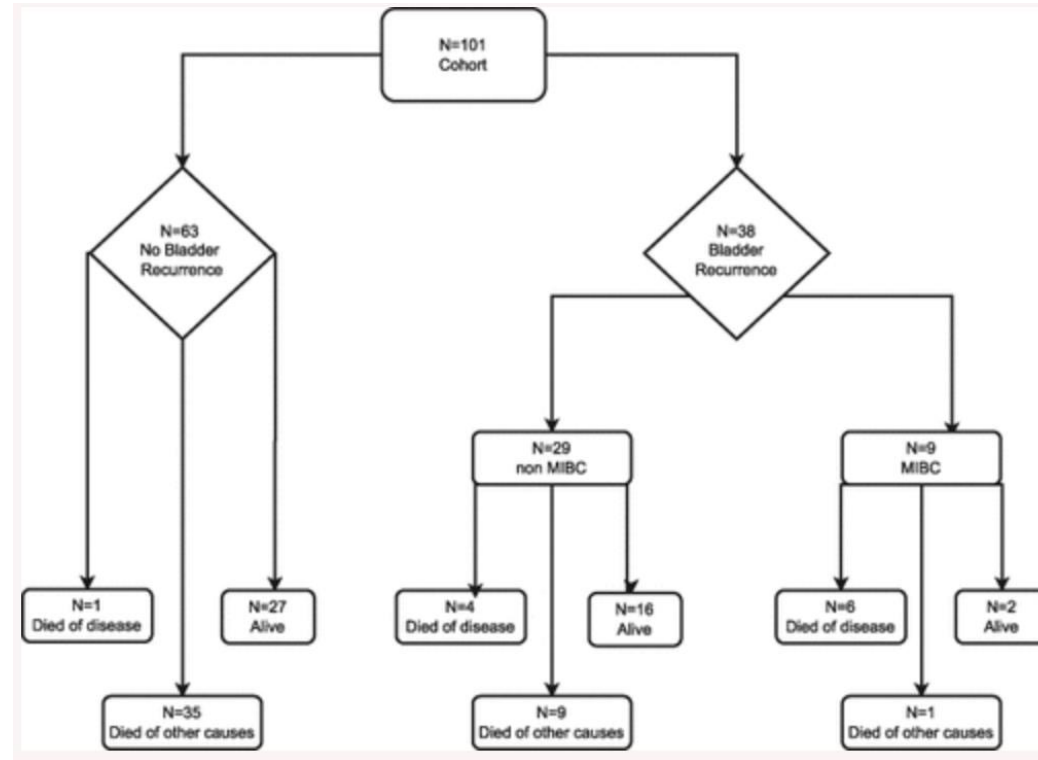
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What is happening to patient after NAT without RC?

- Prospective study
- Highly selected
- cCR post NAC
- 1994 to 2015
- > 10 years of follow-up



- 26% CIS
- 16% LVI

- Among patients who relapsed in the bladder :
 - 5 yr CSS 15%
 - 15 yr CSS 26%

➔ The risk of recurrence persisted beyond 10 yrs !

Do we have CONVINCING prospective evidence?

Major Inclusion Criteria:

- cT2-T3 N0M0
- ECOG 0-1
- Urothelial Predominant Histology

Not a randomized trial

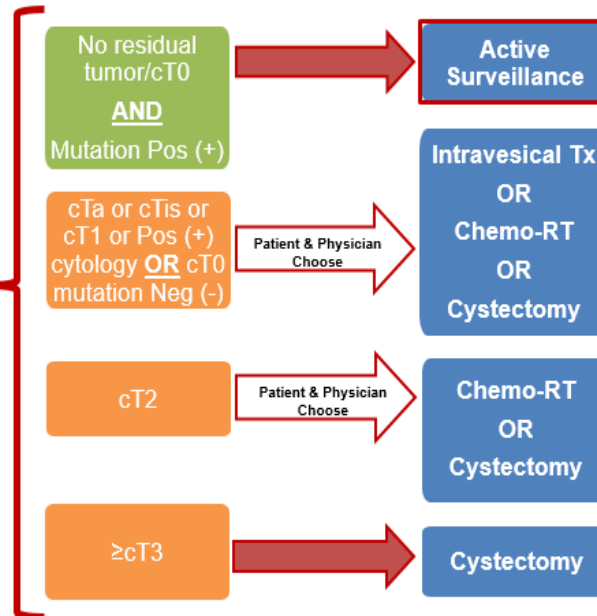


Sequencing (Caris)

Mutation positive defined as any alterations in:

- ATM
- RB1
- FANCC
- ERCC2

RETAIN-1



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

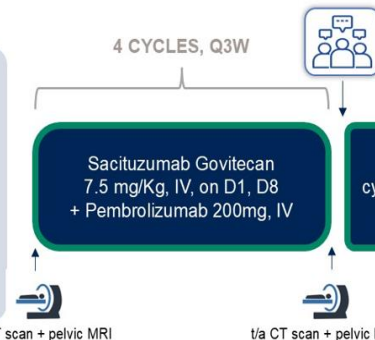
SURE-02

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

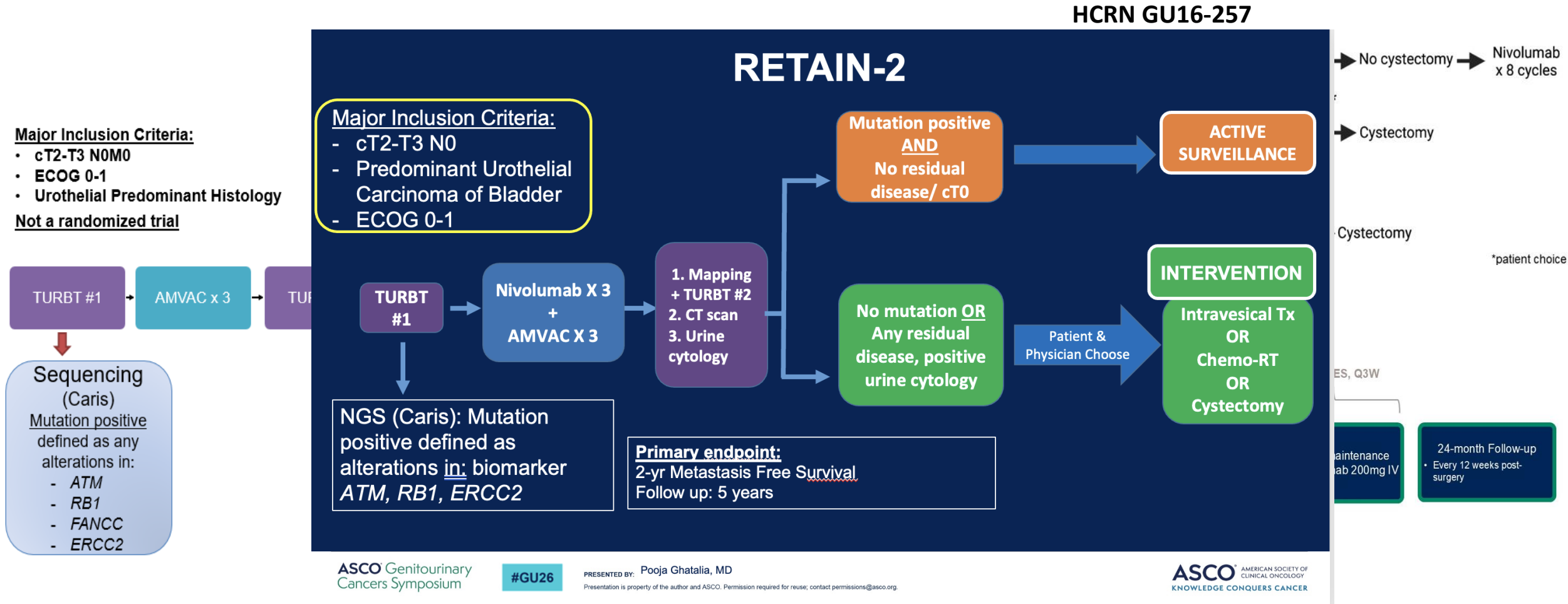
4 CYCLES, Q3W



13 CYCLES, Q3W

- Geynisman DM, *et al.* *J Clin Oncol.* 2025;43(9):1113–1122; Ghatalia P, *et al.* *J Clin Oncol.* 2025;43(5_suppl):815; Galsky MD, Daneshmand S, Izadmehr S, *et al.* *Nat Med.* 2023;29:2825–2834.
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Do we have CONVINCING prospective evidence?



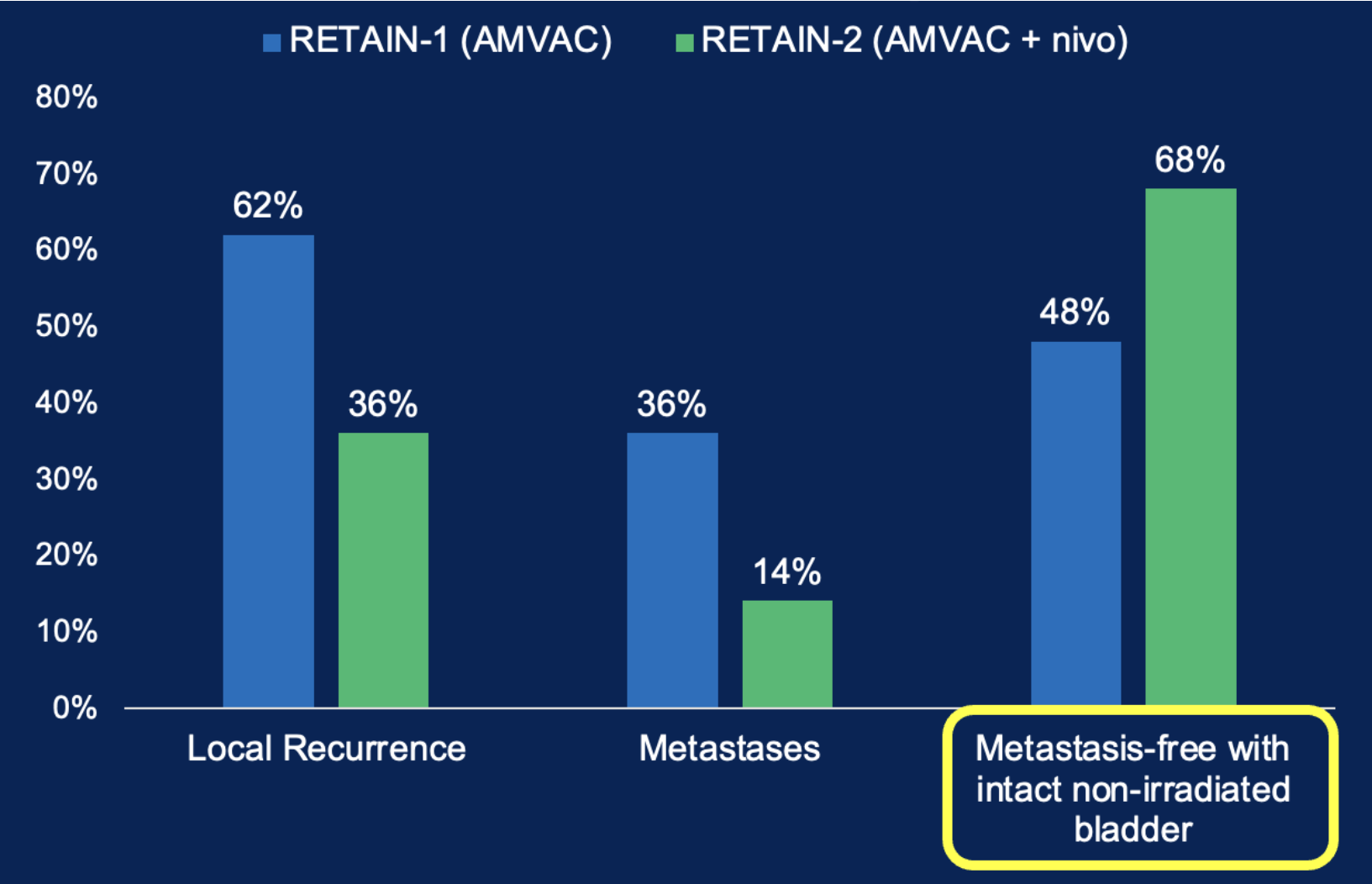
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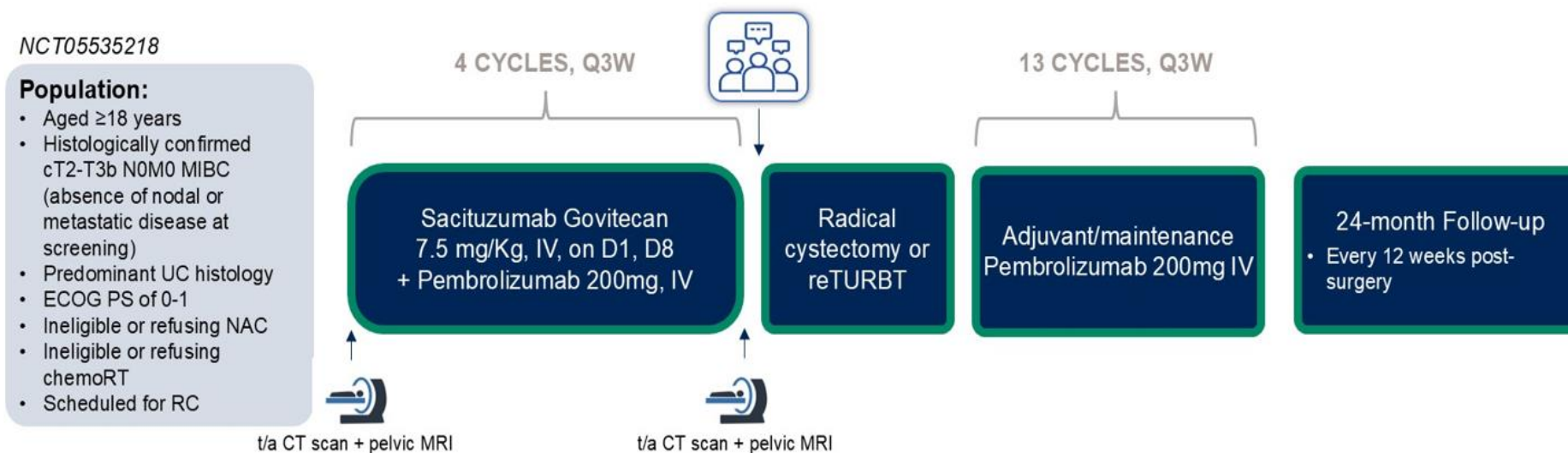
Modern risk adapted approach: making progress

Trial	Selection / regimen	Primary endpoint	Key efficacy signal	Why this still worries me
RETAIN-1	AMVAC; DDR-mutant + cT0 patients placed on active surveillance	2-y MFS for whole cohort	2-y MFS 72.9%; AS subgroup 76%; 25 entered AS	Primary endpoint missed; 68% of AS patients recurred; only 48% kept an intact bladder without metastasis
RETAIN-2	AMVAC + nivolumab; mutation + cCR guided active surveillance	2-y MFS noninferiority design	Estimated 2-y MFS 83.5% overall; 85.2% in AS; 68% of AS patients ended metastasis-free with intact non-irradiated bladder	Still small, nonrandomized, highly selected; in AS cohort: 4 NMIBC recurrences, 3 MIBC recurrences, 1 pelvic nodal recurrence

Comparison of RETAIN-1 vs RETAIN-2 Outcomes in Active Surveillance patients

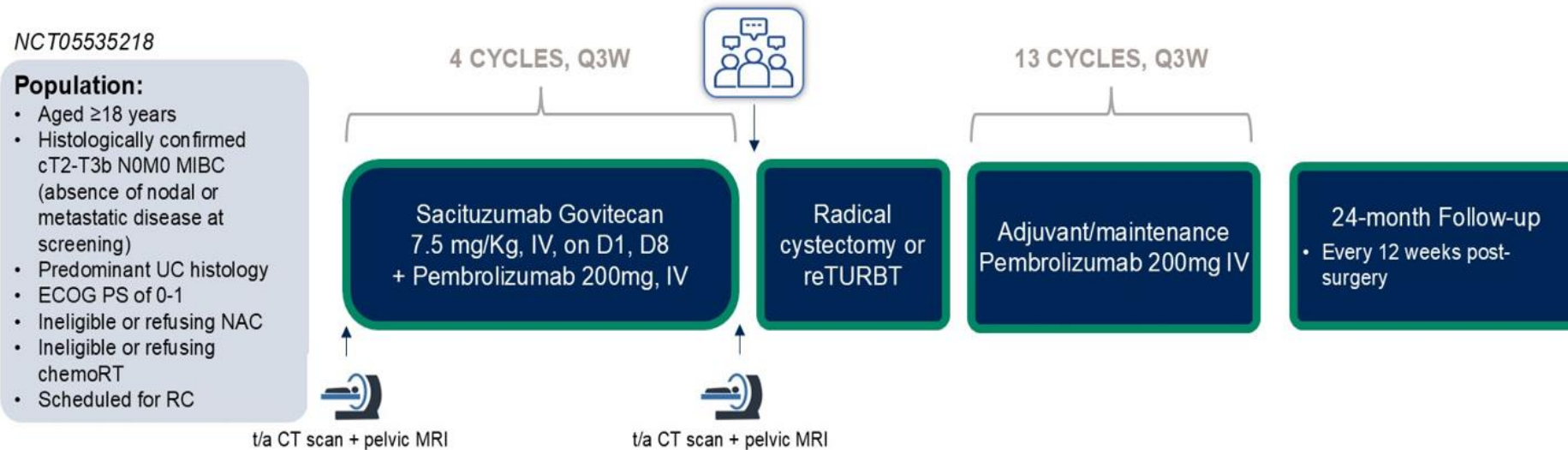


SURE 02 : Interesting again, but too early and not strong enough for routine use



- cCR **39%** (19/49)
- At data cut off, 6 patients with metastatic relapse !

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= 60% needed radical treatment after SG+ Pembro!

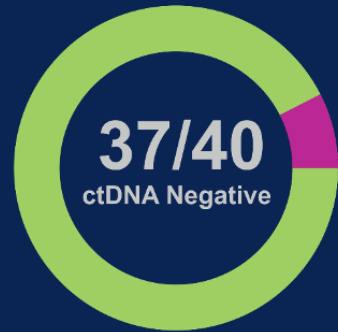
= miss chance of cure????

cCR DOES NOT mean durable disease control !

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Post-NAT ctDNA status predicts **metastatic control** but **not local control** in Active Surveillance patients

Post-treatment ctDNA Status
Among AS Patients (N=40)



■ ctDNA+ (3)
■ ctDNA- (37)

24-Month MFS

82.6%

Metastasis-Free Survival

24-Month RFS

51.4%

Recurrence-Free Survival

RFS is driven by
local recurrence

Patients managed with Active Surveillance: **N=40**



Patients who developed local recurrence: **N=21 (52.5%)**



● Recurred (n=21) ● No recurrence (n=19)

Of those with local recurrence, ctDNA positive: **Only 2 (9.5%)**



● ctDNA Negative (n=19) ● ctDNA Positive (n=2)

**All metastatic events were
preceded by local recurrence**

Conclusion

- ❌ Clear criteria for patient selection
- ❌ Proper cCR definition
- ❌ Stronger prospective data with durable BI EFS !
- ❌ Local AND metastatic control
- ❌ Clear salvage solution



Following this debate: On Monday what will be your approach?

65 y/o male with MIBC who underwent NAT and has a normal CT-scan post NAT

- Avoid local treatment
- Go ahead with local treatment

