#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

Management of Perioperative therapy in Muscle-Invasive Bladder Cancer

Andrea Necchi, MD, FASCO
Associate Professor, Vita-Salute San Raffaele University
Director of the Strategic Program of Research in Genitourinary Tumors
IRCCS San Raffaele Hospital, Comprehensive Cancer Center

I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato

UniSR
Università Vita-Salute San Raffaele

Declaration of interests

- Financial interests:
  - Astellas, Steering Committee Member, Personal, Financial interest
  - Astra Zeneca, Research Grant, Institutional, No financial interest
  - Astra Zeneca, Steering Committee Member, Personal, Financial interest
  - Bicycle Therapeutics, Steering Committee Member, Personal, Financial interest
  - BMS, Research Grant, Institutional, No financial interest
  - BMS, Steering Committee Member, Personal, Financial interest
  - Catalym, Coordinating PI, Personal, Financial interest
  - Daiichi Sankyo, Steering Committee Member, Personal, Financial interest
  - Genenta Sciences, Coordinating PI, No financial interest
  - Gilead, Research Grant, Institutional, No financial interest
  - Gilead, Steering Committee Member, Personal, Financial interest
  - Incyte, Coordinating PI, No financial interest
  - Ipsen, Research Grant, Institutional, No financial interest
  - Janssen, Steering Committee Member, Personal, Financial interest
  - Merck, Research Grant, Institutional, No financial interest
  - Merck, Steering Committee Member, Personal, Financial interest
  - Samsung Bioepis, Funding, Personal, Financial interest
- Non-Financial Interests
  - Global society of Rare Genitourinary Tumors (GSRGT), Leadership Role

Unmet Needs Across the Disease Spectrum

- Only one-third of patients with **NMIBC** receive IVS BCG according to guidelines[1]
- Many of those with **NMIBC** who are unresponsive to BCG experience recurrence or progression[2]

- Close to half of patients with **MIBC** worldwide may not receive curative-intent therapy[3]
- Patients who have undergone RC for **MIBC** often have impaired HRQoL and a high risk of recurrence[4,5]

- More than half of patients with **mUC** may not receive 1L systemic treatment[6,7]
- Many patients with **mUC** who progress on 1L or 2L therapy do not receive subsequent treatment[6,7]

- Development of effective, safe, and durable IVS treatment remains a critical unmet clinical need for patients who want to avoid RC
- Effective approaches post-RC are key to lowering the risk of recurrence
- Strategies for treatment sequencing after metastatic progression are needed
- Clinical trial enrollment allows for modern advances to reach patients

1L, first line; 2L, second line; BCG, bacille Calmette-Guérin; HRQoL, health-related quality of life; IVS, intravesical; MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma;
NMIBC, non–muscle-invasive bladder cancer; RC, radical cystectomy.

1. Tyson M, et al. J Clin Oncol. 2019;37(suppl 15):e16012; 2. Shore ND, et al. Urol Oncol. 2021;39:642-663; 3. Westergren DO, et al. J Urol. 2019;202:905-912; 4. Choi H, et al. Transl Androl Urol.
2020;9:2997-3006; 5. Rouprêt M, et al. Eur Urol. 2021;79:62-79; 6. Morgans AK. Ann Oncol. 2021;32(suppl 5):704P; 7. Bilen M. Ann Oncol. 2021;32(suppl 5):701P.

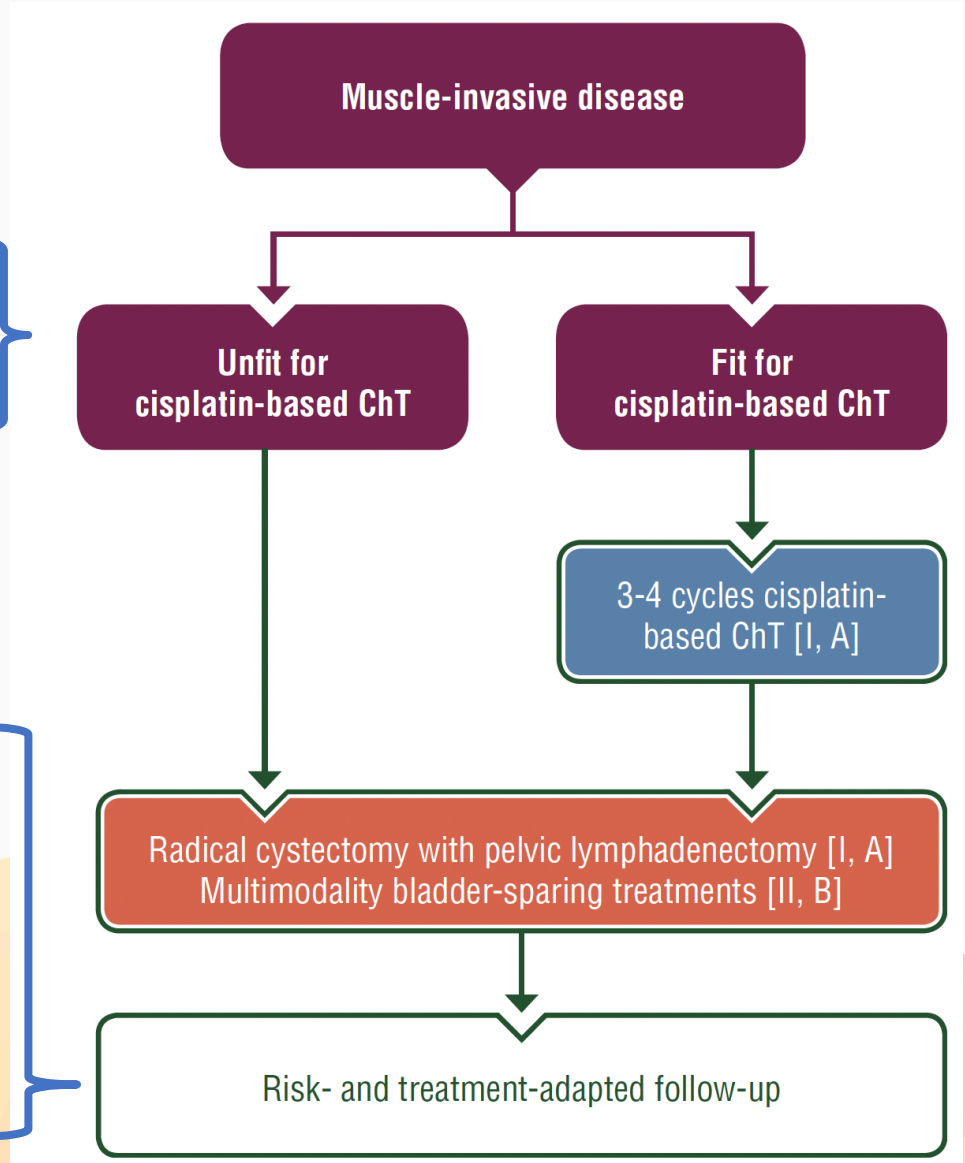
Basic principles guiding a modern approach to patients with MIBC



- MIBC: ~25% de novo + ~20% progressing from NMIBC (implications for therapeutic attrition (impact of prior IO/ADCs exposure on subsequent strategies)[1,2]
- The (old) pardigm of cisplatin eligibility: 50% of pts with MIBC slated to start neoadjuvant chemotherapy
  - Expanding eligibility of neoadjuvant therapies due to IO/ADC use
  - The growing % of chemotherapy refusals due to alternative options
- The evolving paradigm from exclusive neoadjuvant/adjuvant approach to a sandwich strategy (with future implications for surgery)

1. Roviello G, et al. *Nat Rev Urol.* 2024 Oct;21(10):580-592; 2. https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer

Bladder cancer: ESMO Clinical Practice Guidelines are undergoing a profound update



Perioperative EVP (EMA approved)

Adjuvant pembrolizumab (not yet EMA approved)

Adjuvant atezolizumab in ctDNA+ (not yet EMA approved)

Perioperative Durvalumab-GC is recommended and EMA-approved

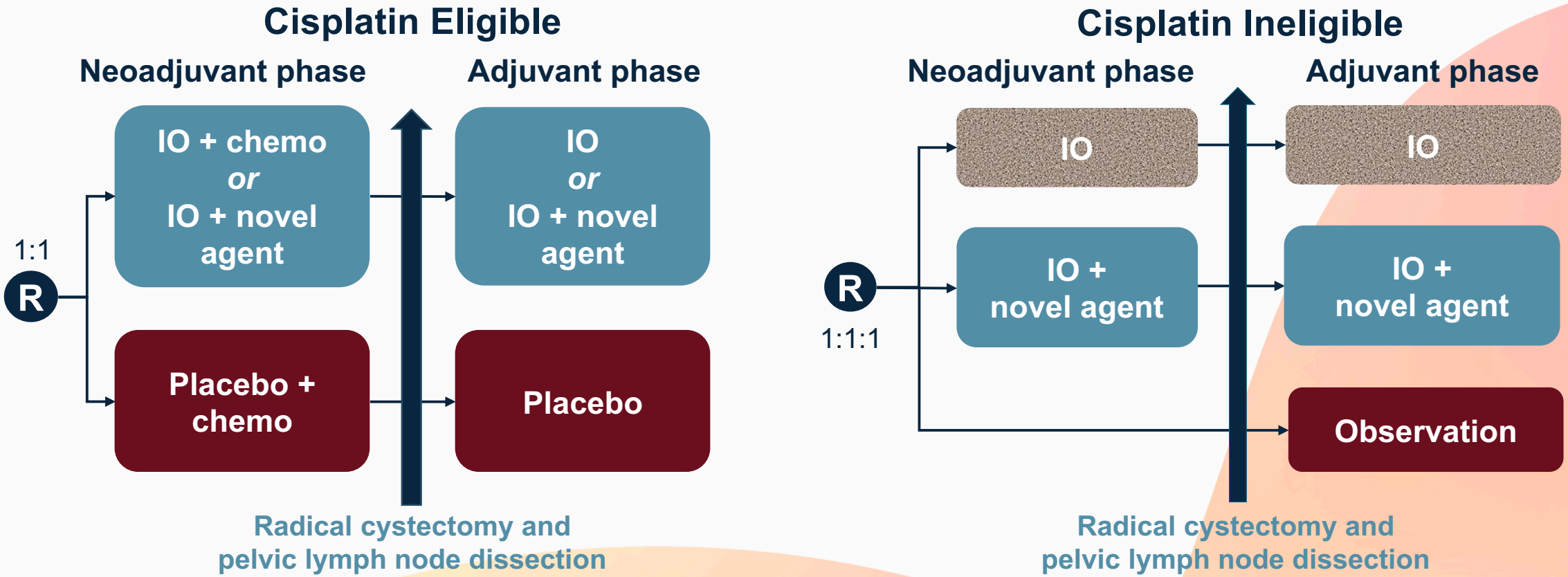
Neoadjuvant dose-dense MVAC vs GC: an ongoing debate

Adjuvant nivolumab is recommended in PD-L1+ high-risk MIBC in EU (EMA-approved)

GUARD CONSORTIUM

Powles T, et al. *Ann Oncol.* 2022;33(3):244-258

Typical design of Phase 3 trials with a blinded approach, assuming a sandwich therapy was appropriate

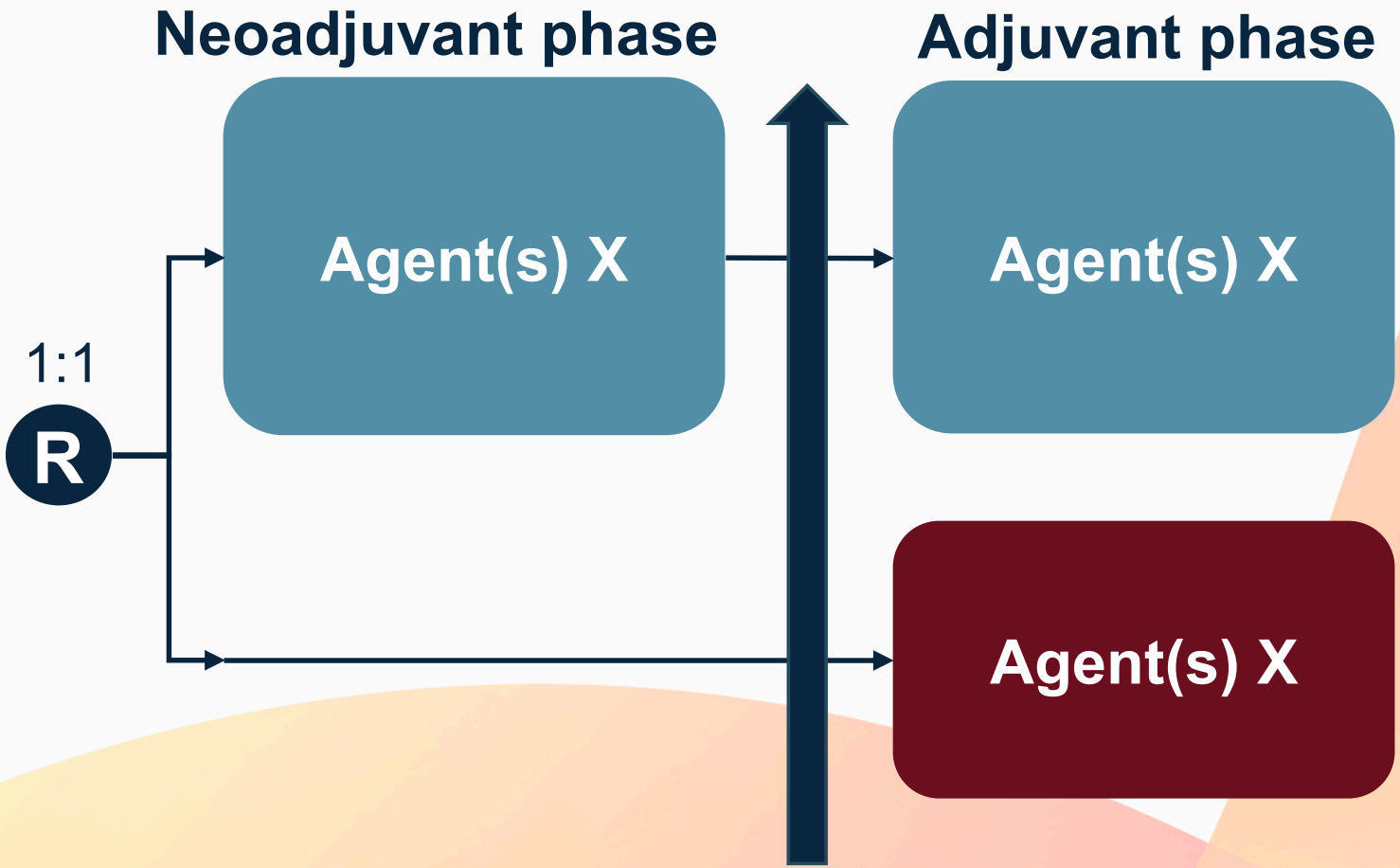


- ENERGIZE (CA017-078): NCT03661320
- KEYNOTE-866: NCT03924856

VOLGA: NCT04960709

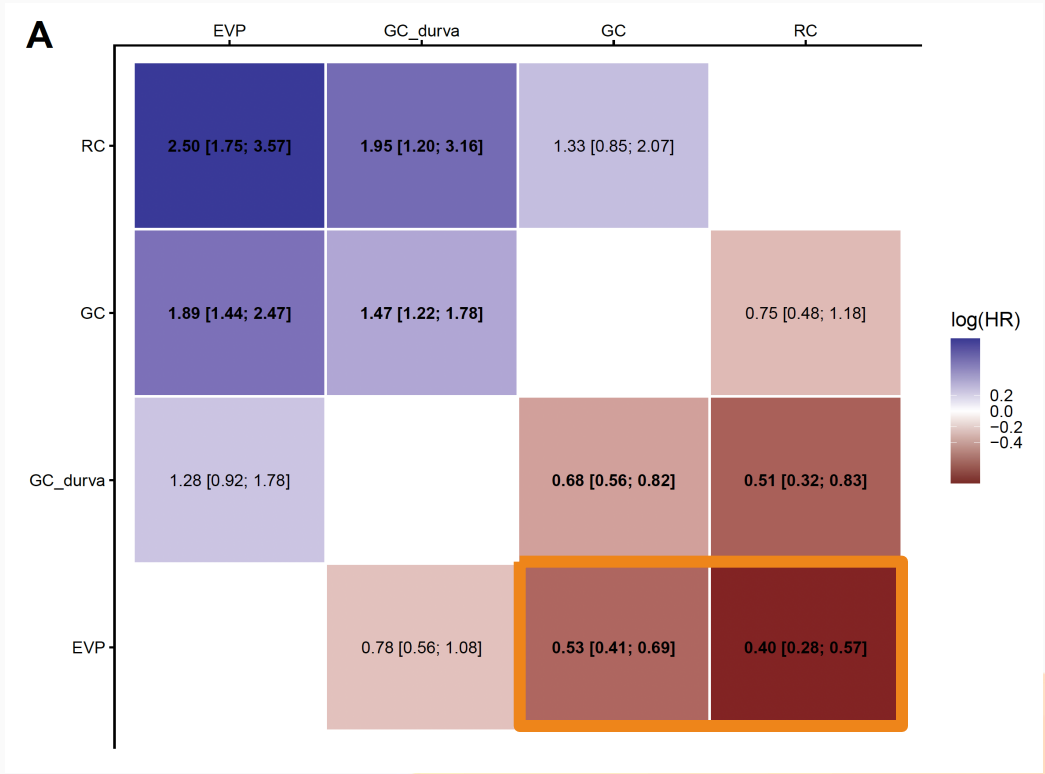
https://www.astrazeneca.com/media-centre/press-releases/2026/imfinzi-ev-improves-efs-os-in-bladder-cancer.html

A missing opportunity for GU academic research

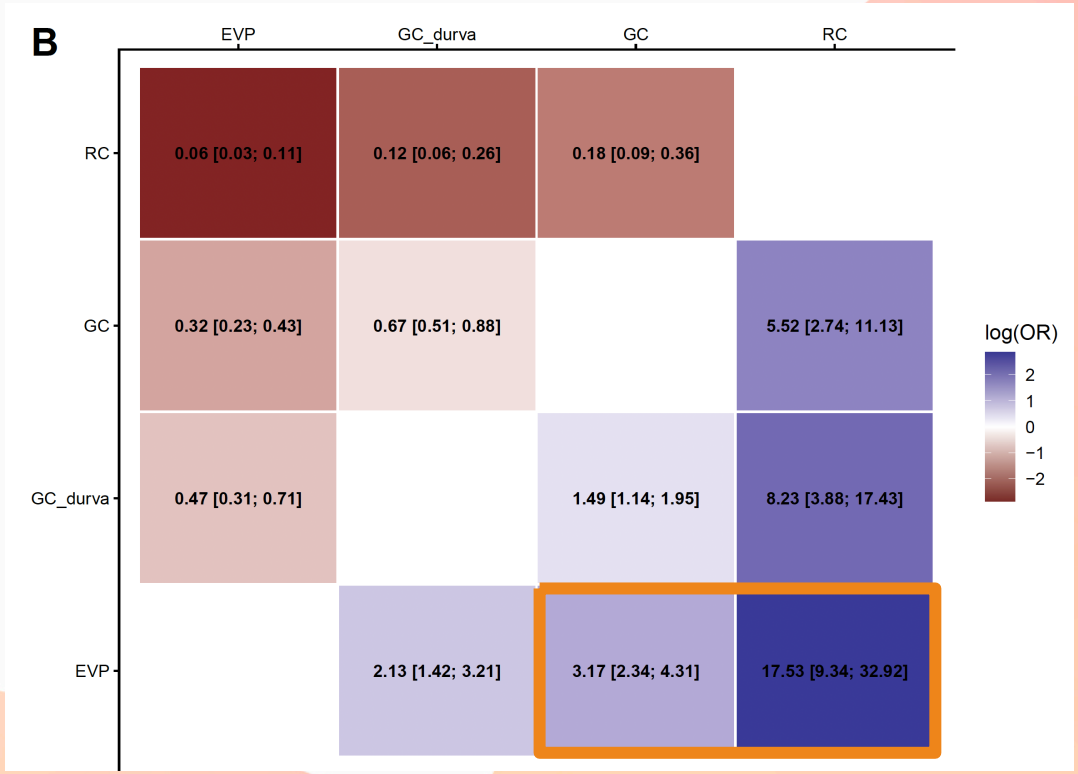


Comparative efficacy of perioperative therapy strategies: A Network Meta-analysis

EFS Hazard Ratios



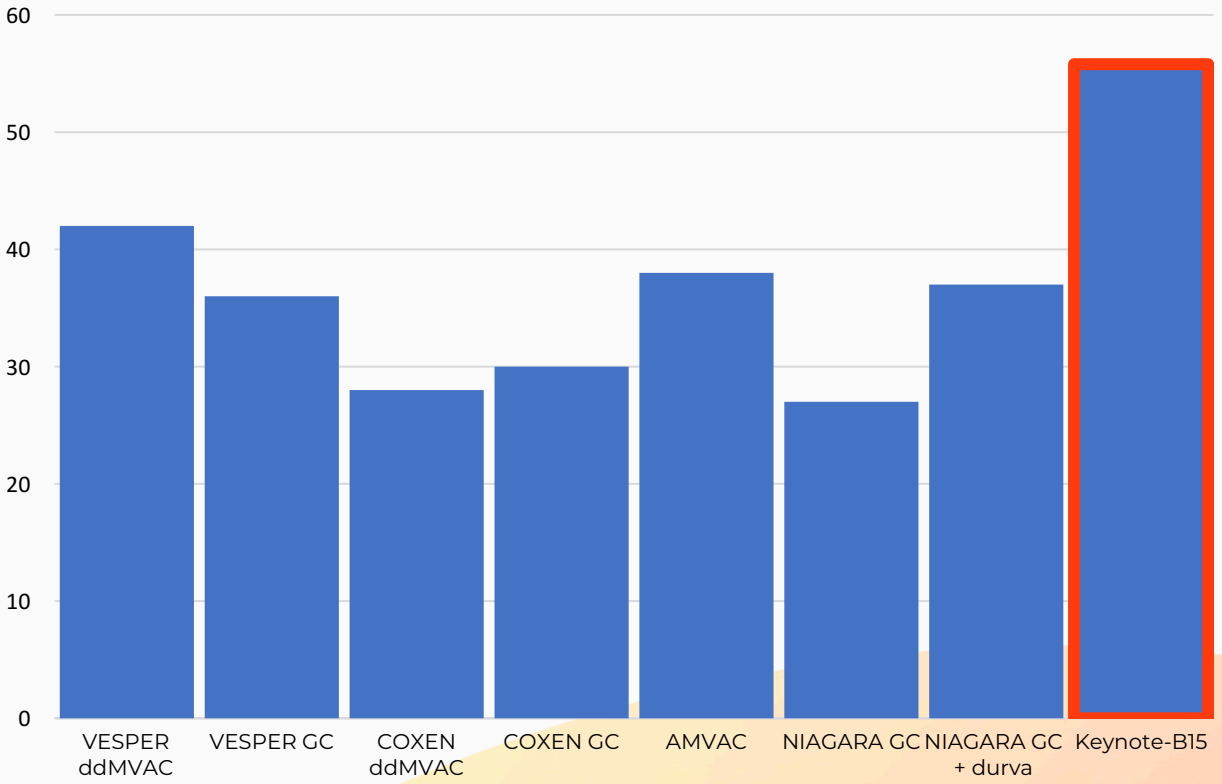
pCR Odds Ratios



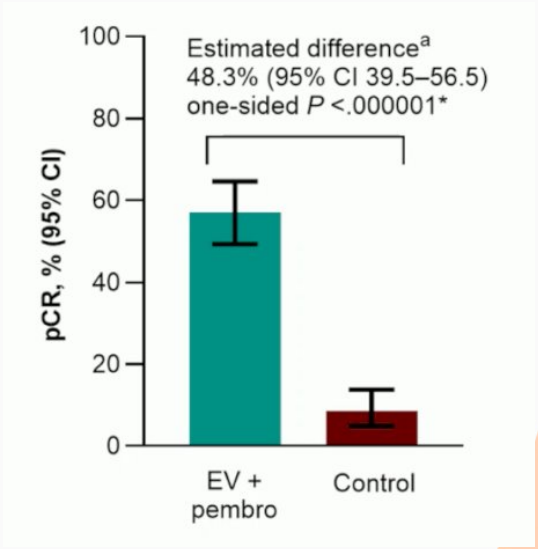
Maiorano BA, et al. ESMO Open. 2026 Aug;11(8):108329. doi: 10.1016/j.esmoop.2026.108329. Epub 2026 Jul 22.

Pathological complete response rates reveal the best systemic therapy options for future strategies - 1

Benchmark pCR % obtained with Chemo+/- IO[1-5]

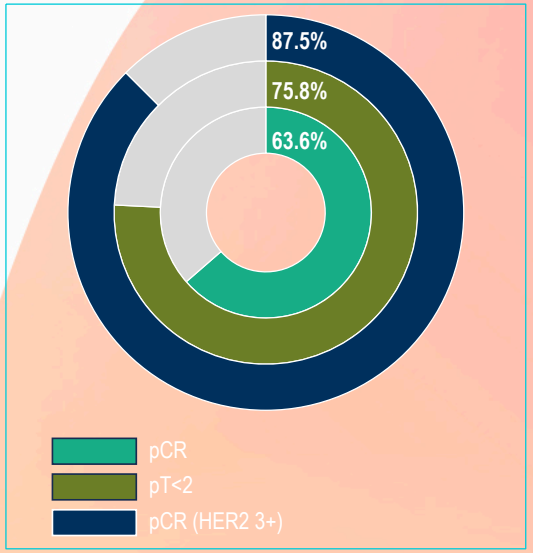


KEYNOTE-905/ EV-303 Trial



Vulsteke C, et al. NEJM 2025

RC48-C017 trial Perioperative DVT



Adapted from Sheng X, et al. GU ASCO 2025 (Abstract. 665)

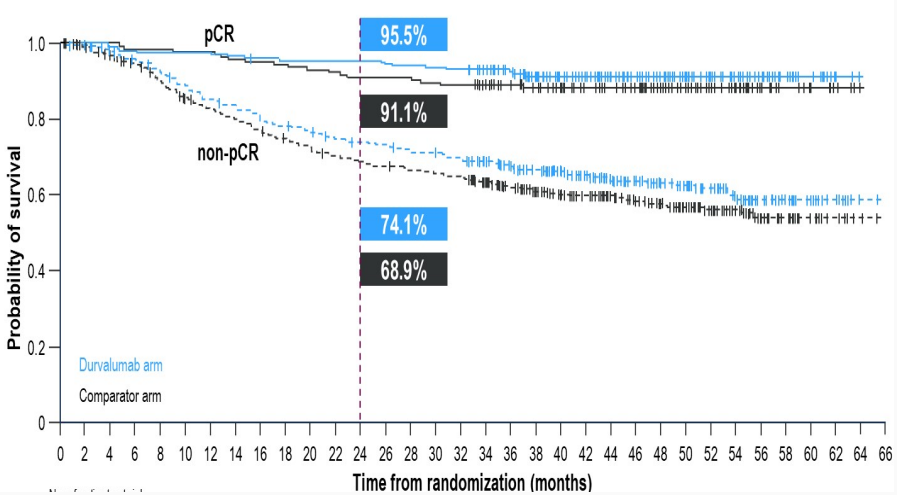
#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

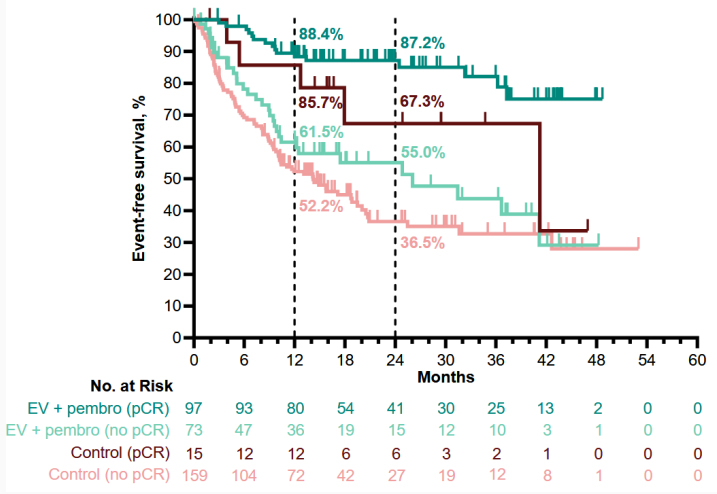
1. Pfister C, et al. *Lancet Oncol.* 2024 Feb;25(2):255-264; 2. Flaig TW, et al. *Eur Urol.* 2023 Sep;84(3):341-347; 3. Plimack ER, et al. *J Clin Oncol.* 2014 Jun 20;32(18):1895-901; 4. Powles T, et al. *N Engl J Med.* 2024 Nov 14;391(19):1773-1786; 5. Galsky MD, et al. ASCO-GU 2026.

Overall Survival in pCR and Non-pCR subgroups across trials and strategies

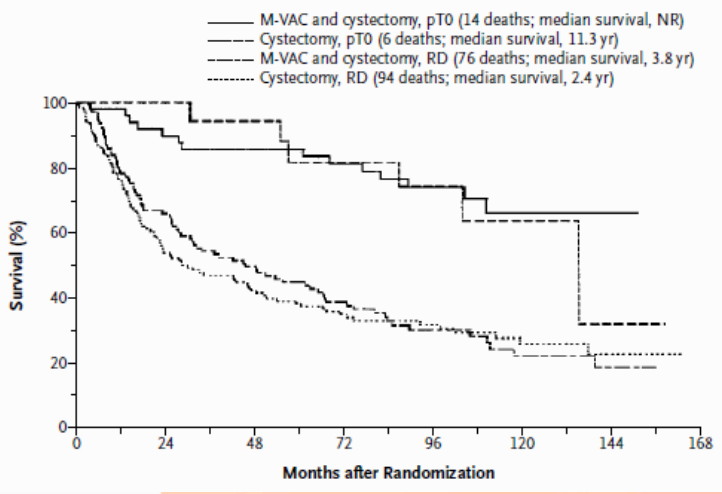
NIAGARA[1]



EV303/KN-905[2]



SWOG-8710[3]

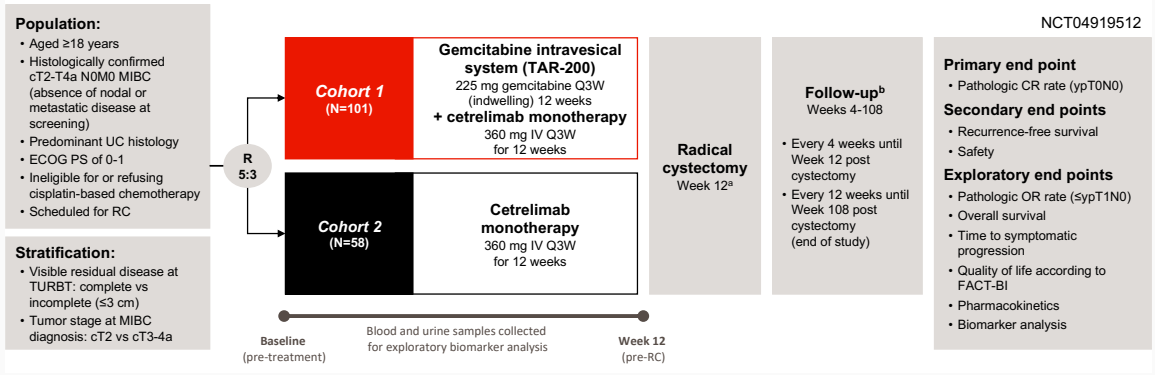


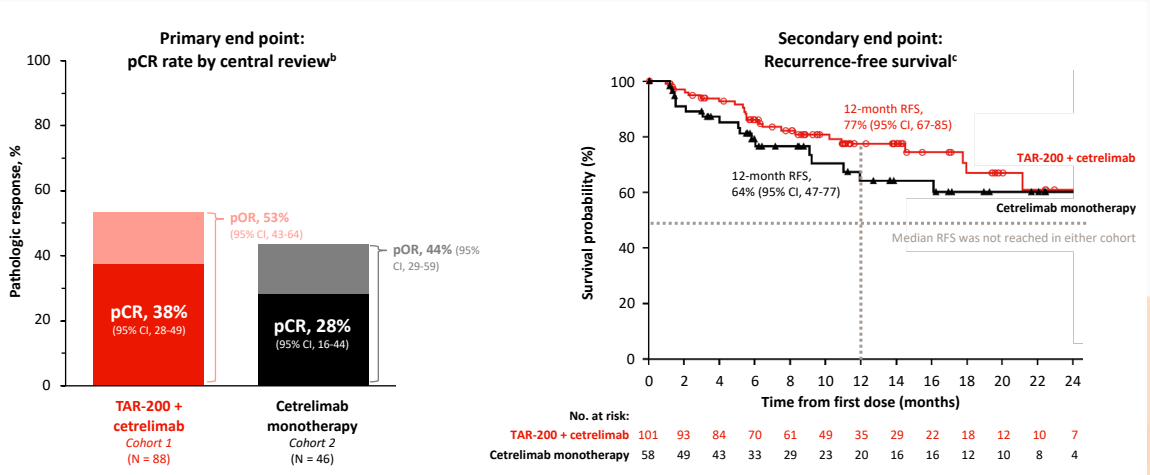
- pCR prognostic regardless of how it is achieved
- Established surrogate of outcome in MIBC
- Improved OS with IO also in non-pCR subgroup
- **Unclear what contribution of adjuvant IO is**
- No predictive biomarkers of response
- No way of extrapolating robust information besides what is implicit in trial design

1. Powles T, et al. N Engl J Med. 2024 Nov 14;391(19):1773-1786; 2. Vulsteke C, et al. N Engl J Med. 2026 Apr 2;394(13):1257-1269; 3. Grossman HB, et al. N Engl J Med. 2003 Aug 28;349(9):859-66.

Combining intravesical and systemic therapy in MIBC:

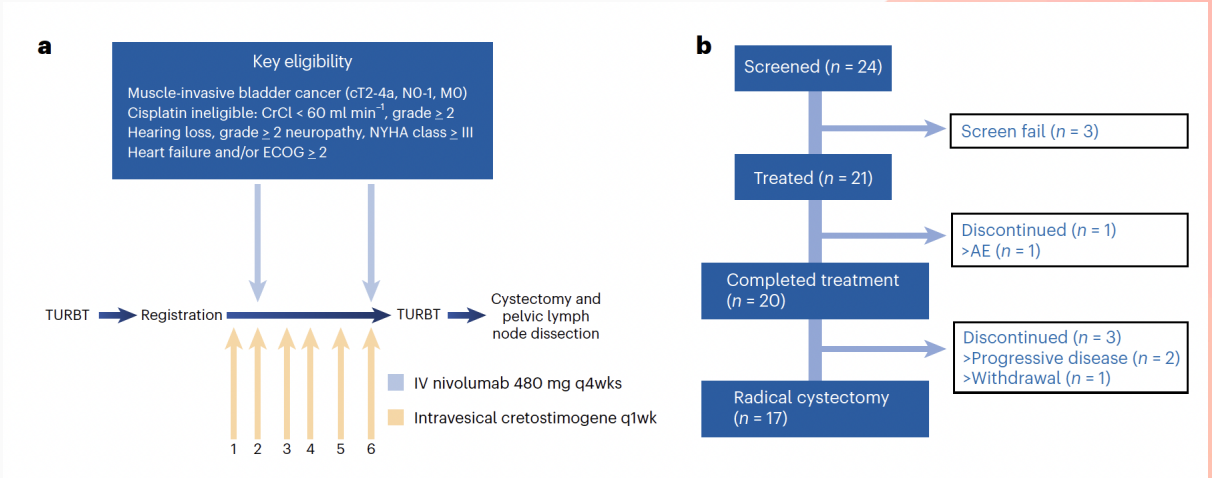
SunRISe-4: Gem-iDRS (TAR-200) + Cetrelimab





Necchi A, et al. Lancet Oncol. 2025 Oct;26(10):1312-1322; J Clin Oncol. 2026 Mar;44(7):586-597.

CORE-002 trial: cretostimogene + nivolumab



- Primary Endpoint: Safety (CTCAE)
- 68% cT2N0 stage
- Chemotherapy refusal for eligibility: 9.5%
- **ypT0N0 rate: 8/19 (42.1%)**
- 1-y RFS rate: 70.4%
- Grade 3-4 TRAE: 57%

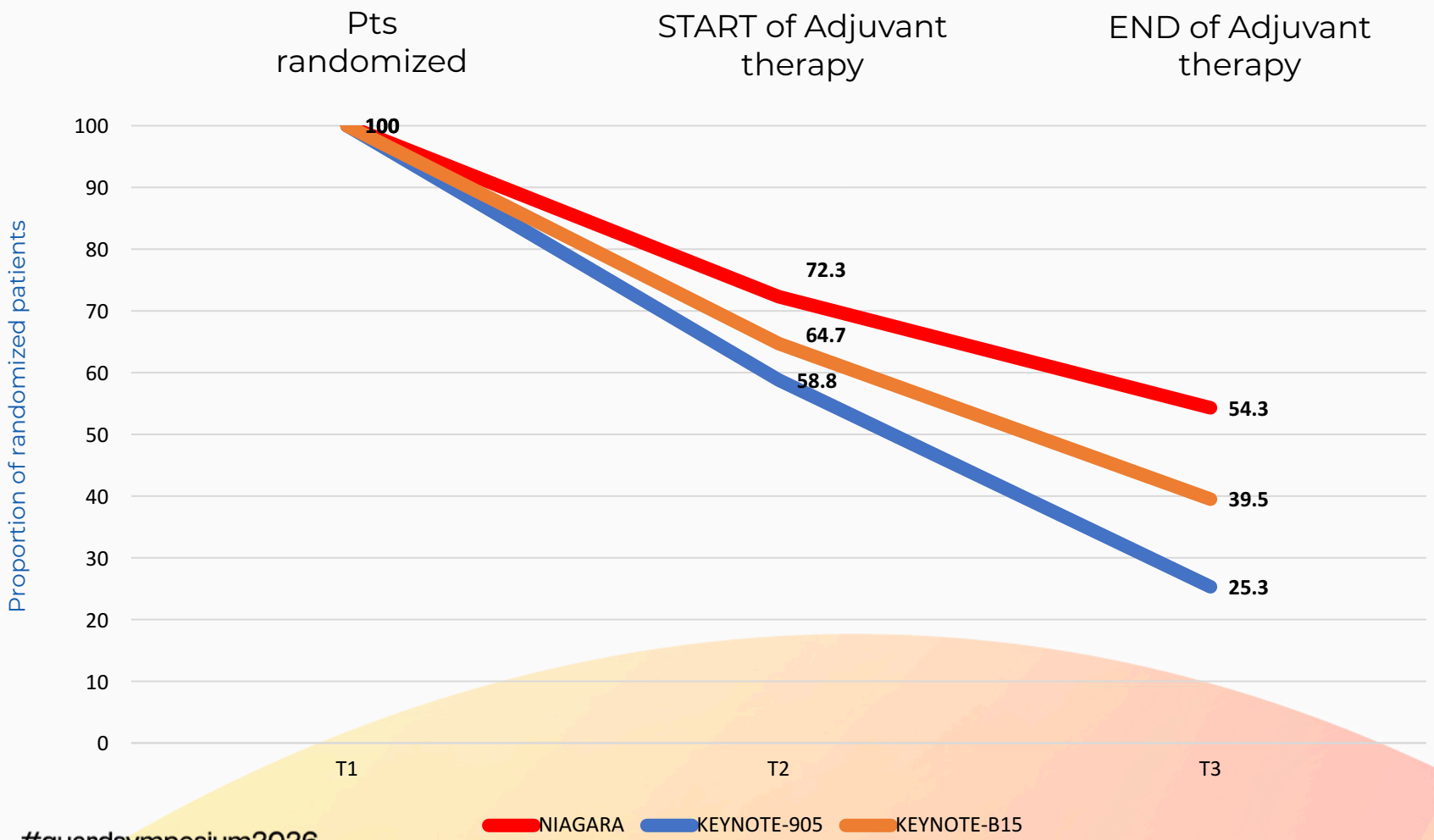
Li R, et al. *Nat Med*. 2025 Jan;31(1):176-188.

#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

Are we ready for treatment de-escalation?

CAVEAT: perioperative systemic therapy attrition in Phase 3 trials



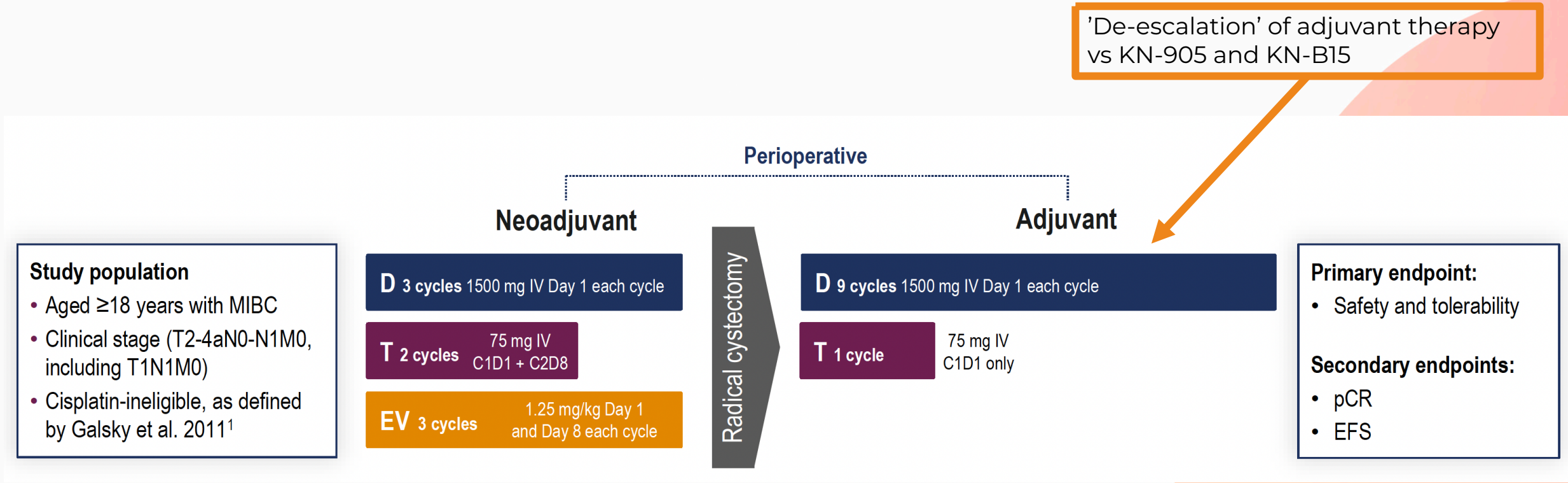
- Inherent bias of unplanned ‘de-escalation’ due to multiple reasons
- Let’s start learning from these limitations when designing an informed de-escalation strategy

#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

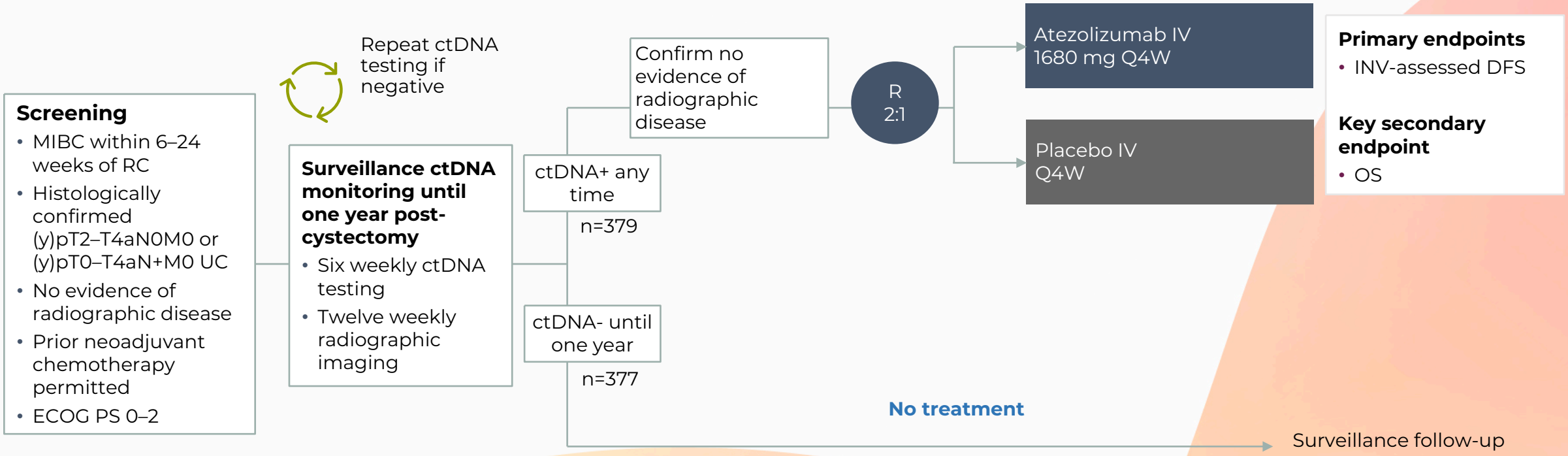
Powles T, et al. *N Engl J Med*. 2024 Nov 14;391(19):1773-1786; Vulsteke C, et al. *N Engl J Med*. 2026 Apr 2;394(13):1257-1269; Galsky MD, et al. *N Engl J Med*. 2026 Jul 23;395(4):338-348

Design of VOLGA study (NCT04960709)



14 May 2026
Positive high-level results reported in a Press Release
https://www.astrazeneca.com/media-centre/press-releases/2026/imfinzi-ev-improves-efs-os-in-bladder-cancer.html

IMvigor011 is a phase 3, global, randomised trial evaluating ctDNA-guided adjuvant atezolizumab vs placebo in patients with MIBC



#guardsymposium2026
@GuardConsortium

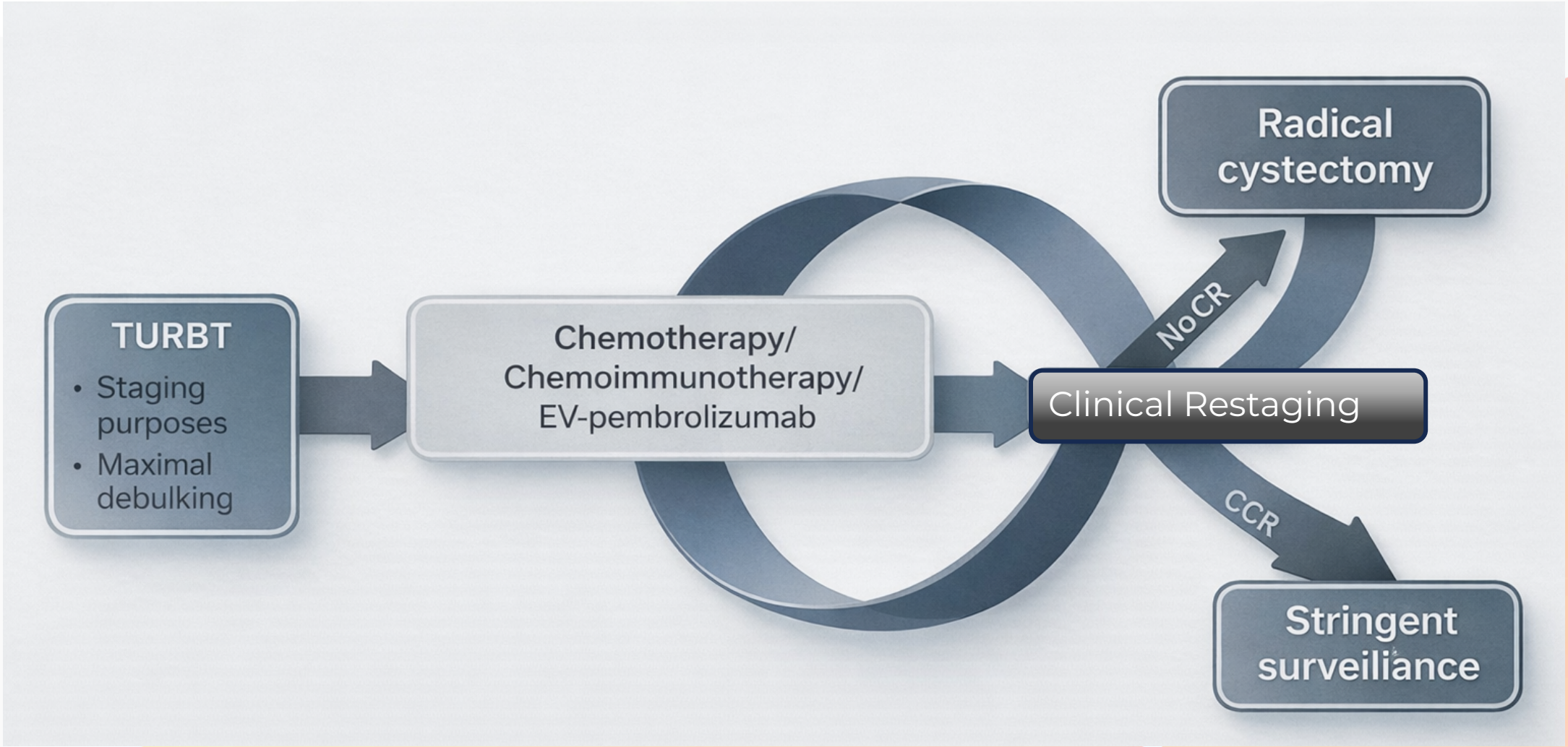
Clinical cut-off: 15 June 2025. ctDNA+ status refers to patients with a positive test who were eligible for randomisation; the positive test could have occurred at any time during the ctDNA monitoring period. ctDNA– status refers to patients with ≥1 negative test result and no positive test result. To be included in the persistently ctDNA– efficacy-evaluable population, patients must have had ≥1 post-baseline clinical outcome assessment and completed 1 y of surveillance or discontinued from surveillance without a ctDNA+ result.

Treatment follow-up for up to one year
UC, urothelial cancer

1. Powles T, et al. Oral presentation at the European Society For Medical Oncology (ESMO); October 17–21, 2025; Berlin, Germany. Abstract LBA8.

GUARD CONSORTIUM

Response-guided bladder sparing approaches



Adapted from Ben-David Trends in Molecular Medicine 2024

Definition of cCR and endpoints for next generation bladder sparing trials

Definition of cCR:

Special Articles

Check for updates

End Points for the Next-Generation Bladder-Sparing Perioperative Trials for Patients With Muscle-Invasive Bladder Cancer

Andrea Necchi, MD[1,2]; Matthew D. Galsky, MD[3]; Nazli Dizman, MD[4]; David H. Aggen, MD[5]; Neeraj Agarwal, MD[6]; Hikmat Al-Ahmadie, MD[7]; Andrea B. Apolo, MD[8]; Leslie Ballas, MD[9]; Rick Bangs, MS[10]; Peter C. Black, MD[11]; Maurizio Brausi, MD[12]; Giorgio Brembilla, MD[13]; Liang Cheng, MD[14,15]; Arturo Chiti, MD[1,16]; Alessia Cimadamore, MD[17]; Maurizio Colecchia, MD[1,18]; Siamak Daneshmand, MD[19]; Savino Di Stasi, MD[20,21]; Jason A. Efstathiou, MD[22]; Alex Filicevas, MS[23]; Daniel M. Geynisman, MD[24]; Petros Grivas, MD[25]; Shilpa Gupta, MD[26]; Alexia Iasonos, MD[27]; Nick D. James, MD[28,29]; Seth P. Lerner, MD[30]; Yohann Loriot, MD[31]; Lydia E. Makaroff, MS[23]; Fernando Maluf, MD[32,33]; Marco Moschini, MD[34]; Irina Ostrovnaya, MD[27]; Sumanta K. Pal, MD[35]; Elizabeth R. Plimack, MD[24]; Gagan Prakash, MD[36]; Sarah P. Psutka, MD[37]; Jonathan E. Rosenberg, MD[5]; Sarmad Sadeghi, MD[38]; Bogdana Schmidt, MD[39]; Lawrence H. Schwartz, MD[40]; Guru P. Sonpavde, MD[41,42]; Marie-Pier St Laurent, MD[11]; Dingwei Ye, MD[43]; Philippe E. Spiess, MD[44]; and Ashish M. Kamat, MD[45]

DOI https://doi.org/10.1200/JCO-25-01608

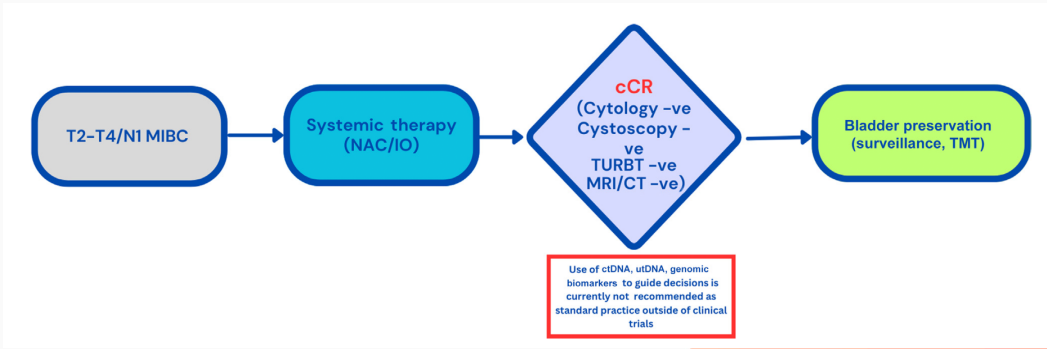


MILAN CRITERIA for cCR consensus definition:

- Negative biopsy
- Negative cytology
- Negative imaging

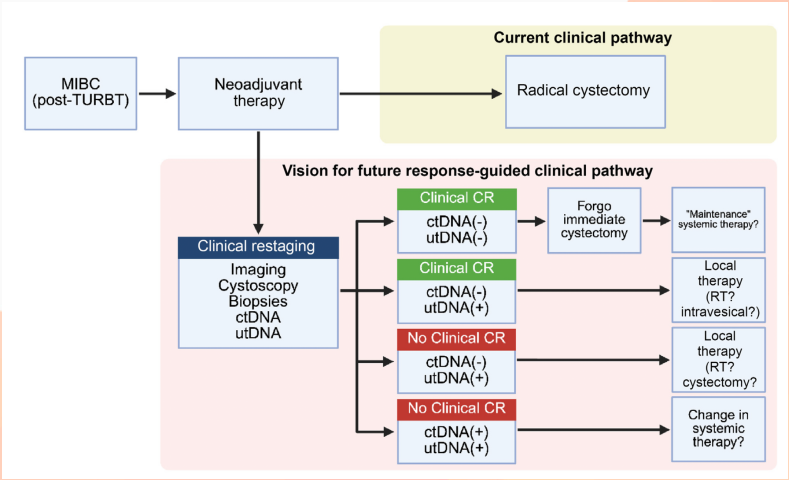
Necchi A, et al. *J Clin Oncol*. 2025 Nov 10;43(32):3536-3544

IBCG recommendations:



Gupta S, et al. Eur Urol. 2026;89:18-28.

Updated expert vision on bladder-sparing approach:



Galsky MD, Necchi A. Eur Urol. 2026 (Epub ahead of print)

#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

Clinical complete response (cCR)

Definition

No evidence of any residual tumor on combined



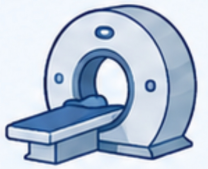
Cystoscopy



TURBT or biopsy



urine cytology



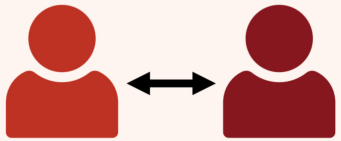
Imaging

Limitation

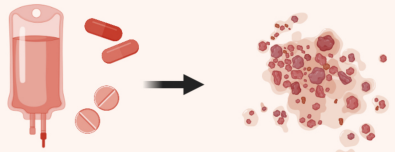
imperfect correlation between pCR due to



Sampling error

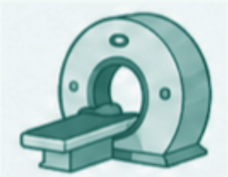


interobserver variability



Treatment-related tissue change

Future refinement



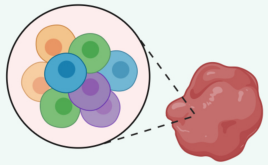
standardization of MRI protocols



AI machine-learning tools



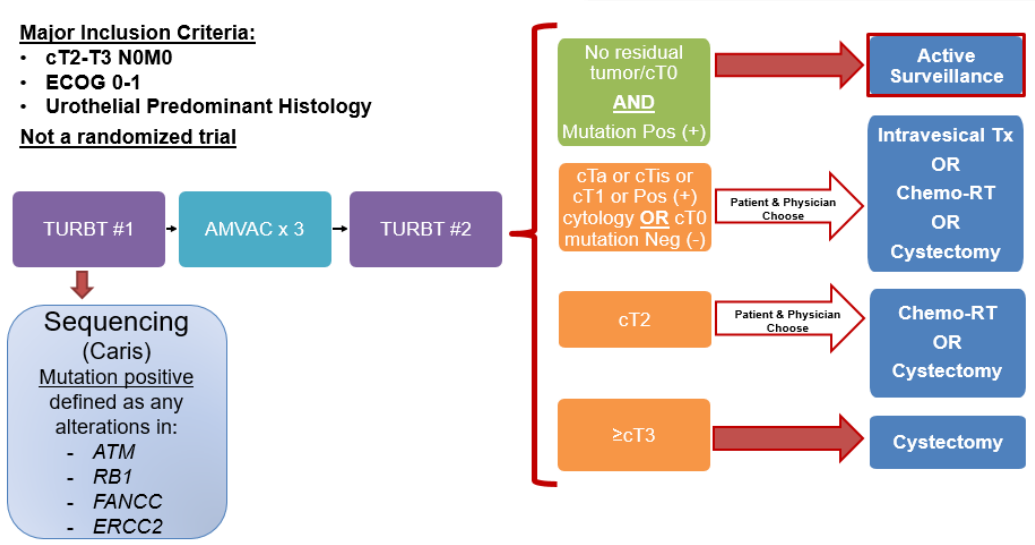
utDNA ctDNA



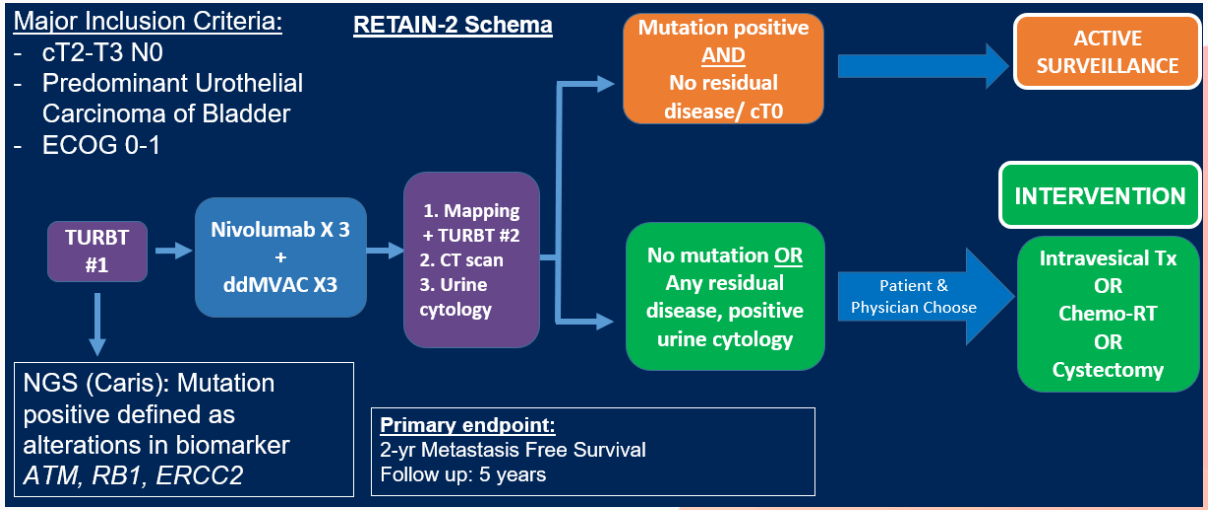
tumor molecular biomarkers

Courtesy: Dr Emanuele Crupi

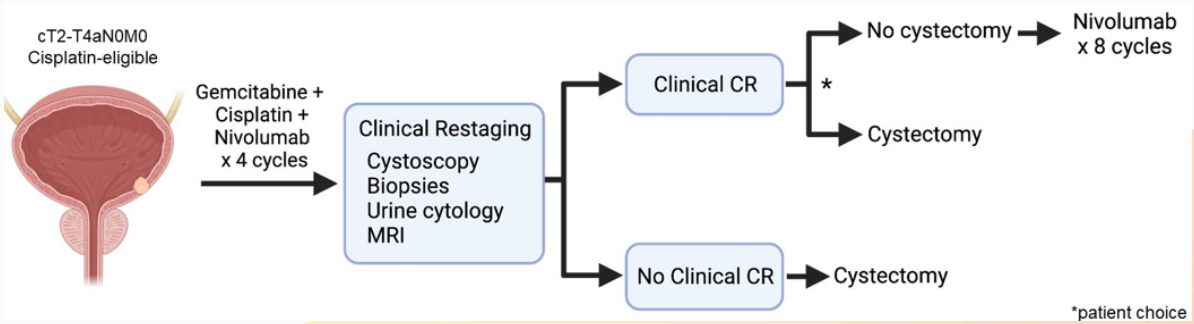
RETAIN-1



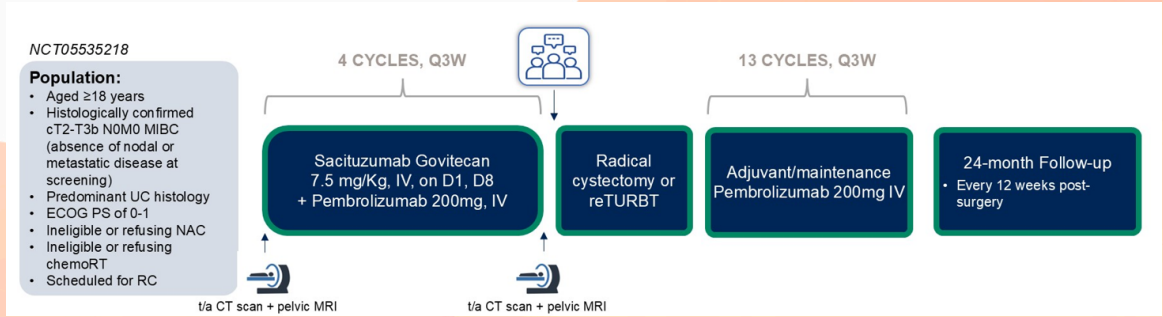
RETAIN-2



HCRN GU16-257



SURE-02



#guardsymposium2026
@GuardConsortium

GUARD CONSORTIUM

Geynisman DM, *et al.* J Clin Oncol. 2025;43(9):1113–1122; Ghatalia P, *et al.* ASCO-GU 2026; Galsky MD, *et al.* Nat Med. 2023;29:2825–2834; Necchi A, *et al.* Lancet Oncol. 2026 Apr;27(4):442-451

Type of recurrences reported in response-adapted, bladder-preserving trials

Study	RETAIN-1[1]	RETAIN-2[2]	HCRN GU 16-257[3]	SURE-02[4]	HCRN GU 20-444[5]
N	70	71	76	49	46
Patients allocated to retaining bladder under active surveillance N (%)	25 (36)	22 (31)	33 (43)	29 (59)	19 (43)
Median duration of follow-up (months)	40.4	34.7	47	14	11
Local recurrence in bladder-preserving group N (%)	16 (64)	10 (45)	14 (42)	2 (7)	1 (5)
Patients developing metastases in bladder-preserving group N (%)	9 (36)	3 (14)	3 (9)	0	0
Patients remaining metastases-free with intact unradiated bladder in the bladder-preserving group N (%)	12 (48)	15 (68.2)	22 (69)	23 (79)	Not reported

1. Geynisman DM, et al. J Clin Oncol. 2025 Mar 20;43(9):1113-1122; 2. Ghatalia P, et al. J Clin Oncol 43, 2025 (suppl 5; abstr 815); 3. Galsky MD, et al. Proc Natl Acad Sci U S A. 2026 Feb 24;123(8):e2533449123; 4. Necchi A, et al. Lancet Oncol. 2026 Apr;27(4):442-451; 5. Anker J, et al. J Clin Oncol 44, 2026 (suppl 7; abstr 737);

Examples of trials of Immunotherapy intensification with RT

Study / registry	N	Treatment / population	Preservation pathway / response assessment	Primary endpoint; main findings
INDIBLADE NCT05200988[1]	50	Induction ipilimumab + nivolumab, then CRT; cT2–T4aN0–2M0 MIBC.	Definitive bladder-preserving CRT after dual ICT; imaging/cystoscopy and exploratory ctDNA monitoring.	**2-y BI-EFS: 78%; 2-y OS 96%**
DUART / BTCRC-GU15-023 NCT02891161[2]	26	Durvalumab + RT, then adjuvant durvalumab; T2–T4N0–2M0, surgery/cisplatin unfit.	Definitive RT plus concurrent/adjuvant durvalumab; imaging and cystoscopic response.	**1-y PFS/DCR: CR 54.5%, 1-y PFS 71.5%**
IMMUNOPRESERVE-SOGUG NCT03702179[3]	32	Durvalumab + tremelimumab + concurrent RT; localized T2–T4N0–2M0 MIBC.	Bladder preservation; absence of MIBC at post-treatment tumour-site biopsy.	**CR rate: 81%; 2-y BI-DFS 65%, OS 84%.**

1. Mellema JJ, et al. Nat Med. 2026 Apr;32(4):1241-1248; 2. Joshi M, et al. J Immunother Cancer. 2023 Feb;11(2):e006551; 3. Garcia-Del-Muro X, et al. Clin Cancer Res. 2025 Feb 17;31(4):659-666.

A case from our clinic: persistent ctDNA+ test within a bladder-saving approach

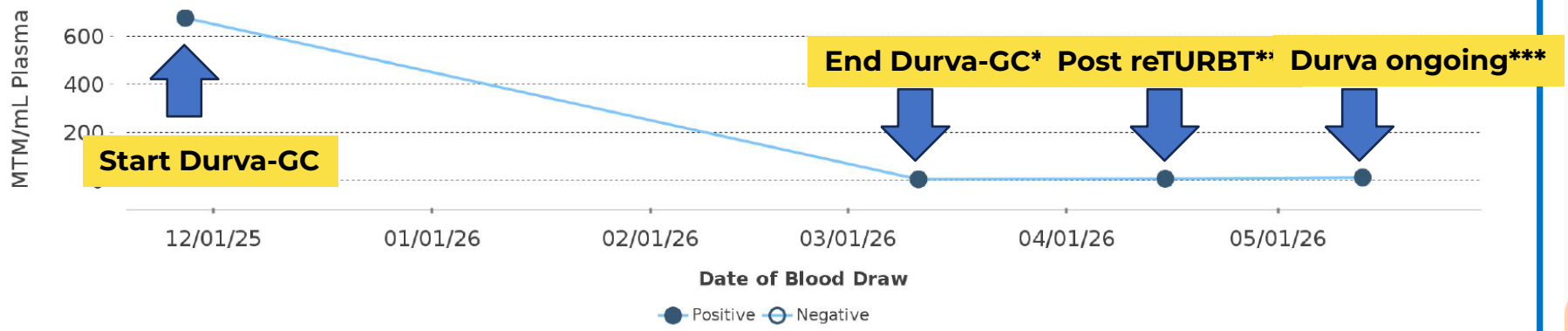
FINAL RESULTS SUMMARY

Signatera Positive ⊕

Date: 05/13/2026
MTM/mL: 11.76

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. See Limitations section below.

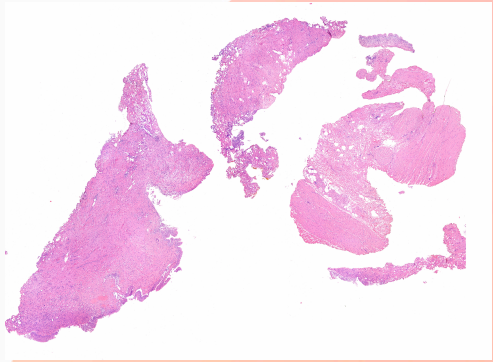
Historical Results



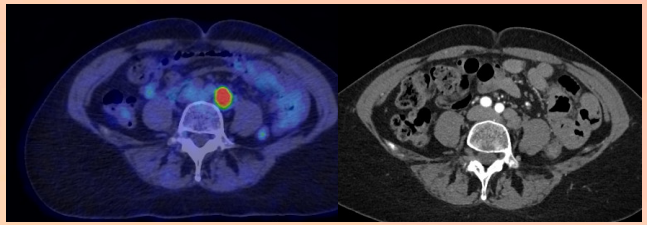
Date	Reported MTM/mL
May 13, 2026	11.76
Apr 15, 2026	6.34
Mar 11, 2026	4.20
Nov 27, 2025	676.17

***Imaging post-Durva GC: cCR**

****reTURBT: ypT0Nx**



*****CT/PET scan: suspicious enlarged retroperitoneal lymph nodes**



Bladder preservation approaches for MIBC[1,2]

SunRISe-2: phase 3 trial of Gem-iDRS (TAR-200) + cetrelimab[a] vs concurrent CRT

N ≈ 550

Key eligibility criteria

- Patients with MIBC
- cT2-T4a, N0, M0
- Not receiving RC

R

1:1

Cetrelimab + TAR-200[b]

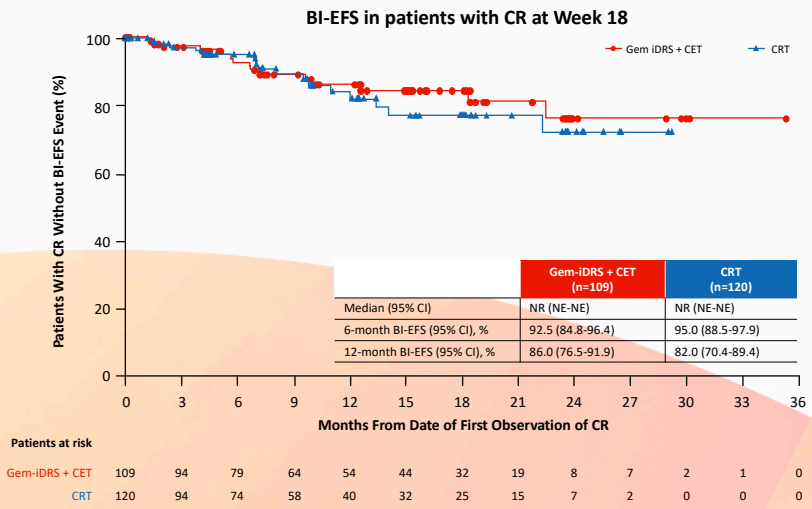
Cis or gem for 6 weeks[c] + radiation therapy[d]

Assessments until histologically proven presence of MIBC, clinical evidence of nodal or metastatic disease[e], RC, death, or end of study, whichever occurs first

Stratification[f]

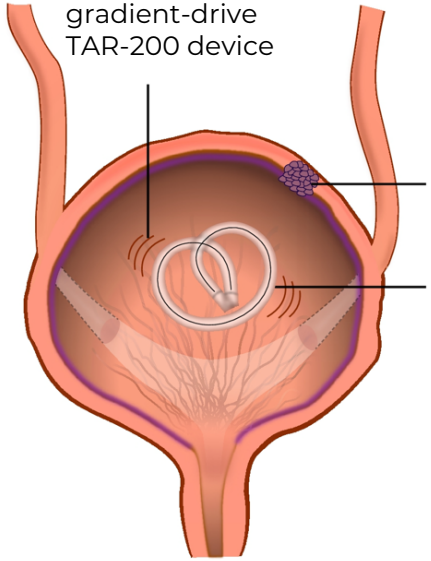
- Completeness (visibly complete vs incomplete [residual tumor < 3 cm])
- Tumor stage (T0 vs Ta/T1/Tis vs T2-T4a)

Primary endpoint: bladder-intact EFS



	Gem-iDRS + CET (n=109)	CRT (n=120)
Median (95% CI)	NR (NE-NE)	NR (NE-NE)
6-month BI-EFS (95% CI), %	92.5 (84.8-96.4)	95.0 (88.5-97.9)
12-month BI-EFS (95% CI), %	86.0 (76.5-91.9)	82.0 (70.4-89.4)

Sustained release of gem by osmotically gradient-drive TAR-200 device



Extracted with permission from Williams.[2]

Necchi A, GU-ASCO 2026

#guardsymposium2026
@GuardConsortium

[a]PD-1 inhibitor. [b]Q3W (indwelling) for first 18 weeks; then starting on week 24, Q12W through study year 3. [c]Investigator's choice cis 35 mg/m^2 QW or gem 27 mg/m^2 Q2W. [d]Investigator's choice of conventional radiotherapy over 6.5 weeks or hypofractionated radiotherapy over 4 weeks. [e]Per RECIST v1.1. [f]Based on screening re-TURBT. Cis, cisplatin; CRT, chemoradiotherapy; EFS, event-free survival; gem, gemcitabine; MIBC, muscle-invasive bladder cancer; PD-1, programmed death-1; Q12W, every 12 weeks; R, randomization; RC, radical cystectomy; TURBT, transurethral resection of a bladder tumor; vs, versus.

1. ClinicalTrial.gov. Accessed July 24, 2024. https://clinicaltrials.gov/study/NCT04658862. 2. Williams SB et al. Presentation at American Society of Clinical Oncology (ASCO) Annual Meeting; June 4–8, 2021; Chicago, IL. Abstract TPS4586.

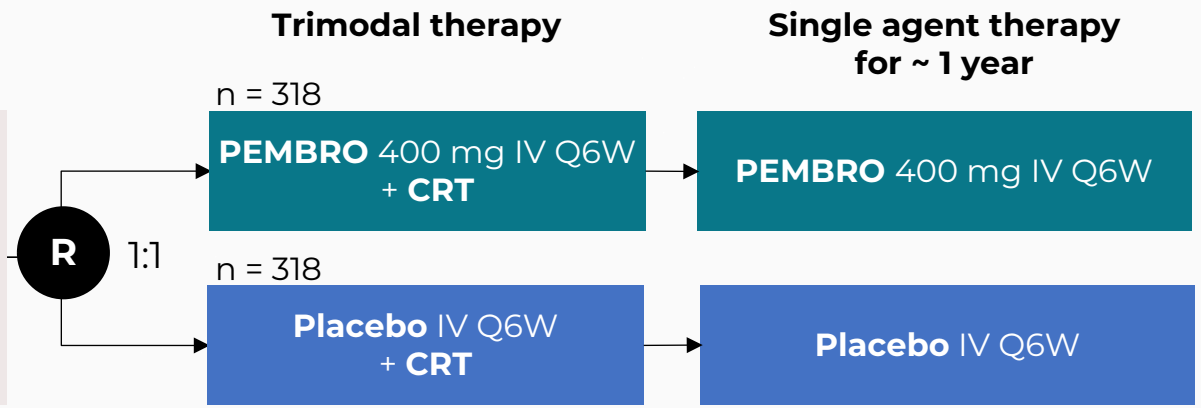
GUARD CONSORTIUM

Harnessing I-O for trimodal therapy in MIBC

KEYNOTE-992: phase 3 trial of PEMBRO + CRT vs CRT

N =

Key eligibility criteria
- MIBC (T2-T4 N0M0)
- Opting for bladder preservation



- Efficacy assessment 10 weeks (± 2 weeks) after CRT[a]
- Efficacy assessment Q12W (± 2 weeks) through year 2 and Q24W (± 2 weeks) beyond year 2[b]

Stratification factors
- ECOG PS (0 or 1 vs 2)
- PD-L1 CPS (< 10 vs ≥ 10)
- T stage (T2 vs T3/4)
- Geographic region (US vs Europe vs ROW)

- **Primary endpoint:** bladder-intact EFS

Extracted with permission from Elsevier from *Eur Urol Focus*, 2023;9:227-228.

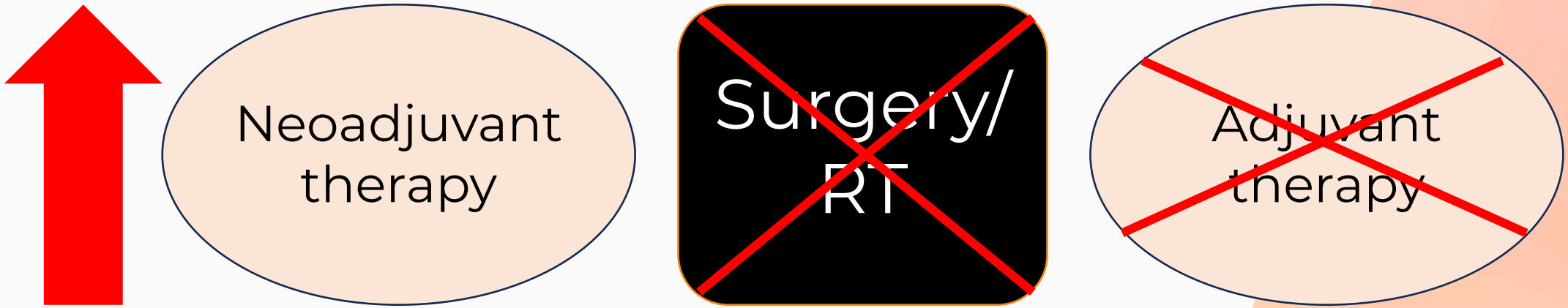
[a]Cystoscopy, urine cytology, biopsy of tumor bed, and imaging. [b]Cystoscopy, urine cytology, biopsy as indicated, and imaging.

CPS, combined positive score; CR, complete response; CRT, chemoradiotherapy; DURVA, durvalumab; EFS, event-free survival; I-O, immuno-oncology; MIBC, muscle-invasive bladder cancer; PD-L1, programmed death ligand 1; PEMBRO, pembrolizumab; PS, performance status; Q6W, every 6 weeks; R, randomization; ROW, rest of world; US, United States; vs, versus.

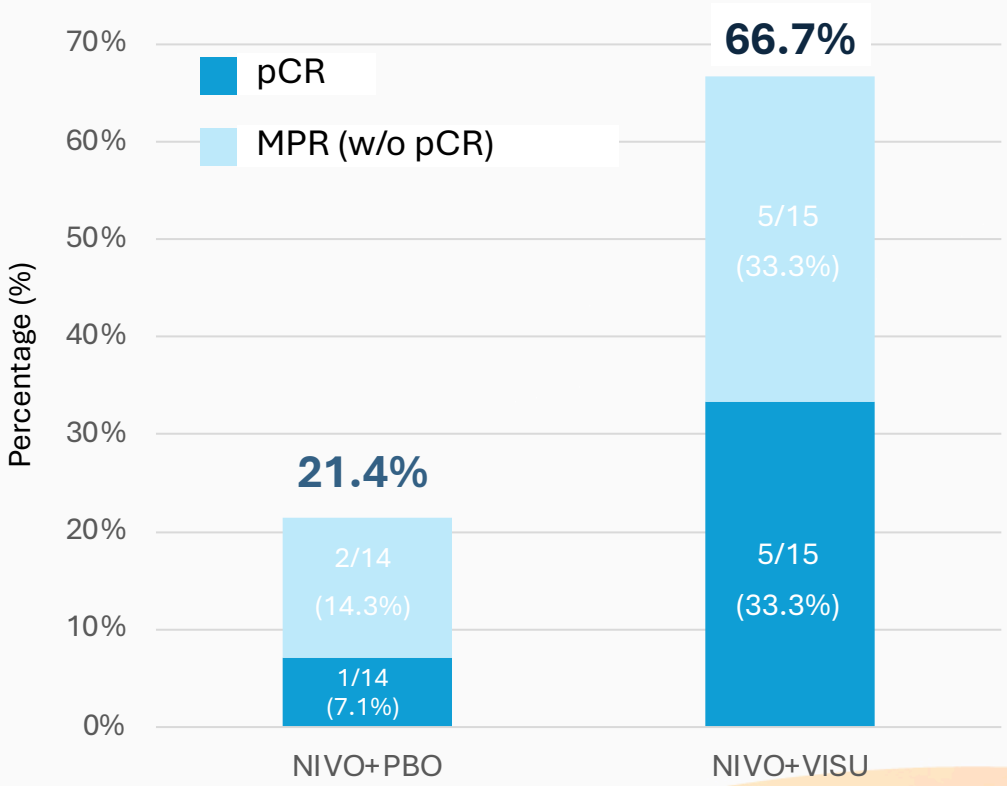
Tissot G et al. *Eur Urol Focus*. 2023;9:227-228.

Ways of further efficacy improvement

EVP + X (concomitant or sequential, IV or intravesical etc.)



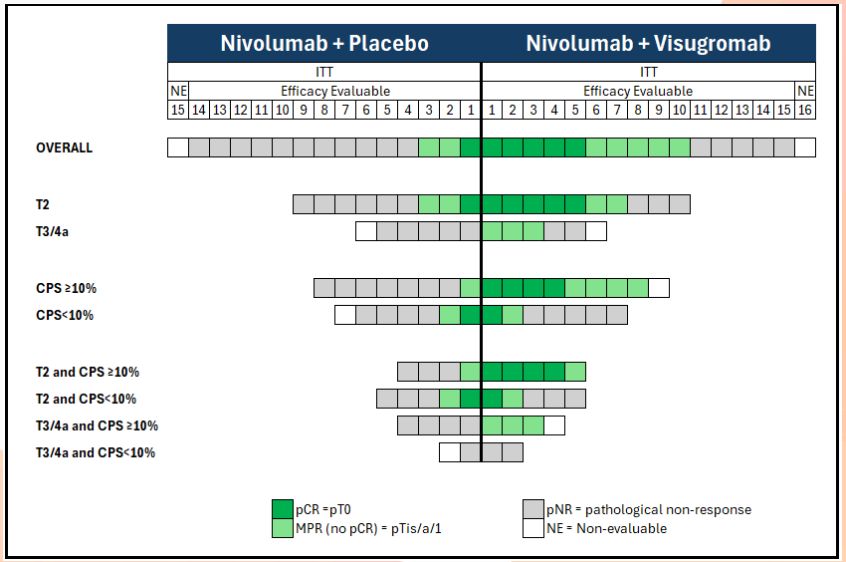
GDFATHER-NEO: Histopathologic response rate was ~3 fold higher in the NIVO+VISU vs NIVO+PBO arm



NIVO+PBO: 1 pCR, 2 MPR, 11 NR*
NIVO+VISU: 5 pCR, 5 MPR, 5 NR

More patients in the NIVO+VISU vs NIVO+PBO arm received bladder-sparing re-TURBT

	NIVO+PBO N=15	NIVO+VISU N=16
Re-TURBT, n (%)	3 (21.4)	6 (40.0)
RC, n (%)	10 (71.4)	9 (60.0)



*Of the 11 patients with NR, 2 patients discontinued early due to toxicity
Of the 31 patients enrolled, 29 were efficacy evaluable.
NR, pathologic non-response; MPR, major pathologic response; pCR, pathologic complete response; RC, radical cystectomy; Re-TURBT, repeat Transurethral Resection of Bladder Tumour

1. Necchi A, et al. Oral presentation at the European Society For Medical Oncology (ESMO); October 17–21, 2025; Berlin, Germany. Abstract LBA110

GUARD CONSORTIUM

Melero I, et al. *Nature* 2024 (ePub ahead of print)

ESMO 2026: Updated Long-term outcomes

Conclusions

- Sandwich (perioperative) therapy remains the standard of care for patients with muscle-invasive bladder cancer (MIBC), supported by level 1 evidence
- Current data do not yet support safe de-escalation of perioperative systemic therapy whenever EVP or Durva-GC is initiated
- Since pCR is achieved in ~35-60% of patients treated with neoadjuvant therapy, a selected cohort of patients may forgo radical cystectomy and remain on stringent surveillance
- Several attemps have been/are being undertaken with the aim of removing the adjuvant or surgical component in selected patients
- Future strategies may focus on building from neoadjuvant EVP backbone






SAVE the DATE

I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato

UniSR
Università Vita-Salute San Raffaele

Comprehensive Cancer Center
IRCCS Ospedale San Raffaele

5th EDITION

SAN RAFFAELE UROLOGIC ONCOLOGY RETREAT

MILAN December 4th, 2026

AULA SAN RAFFAELE - IRCCS Ospedale San Raffaele



EVENTO ECM RESIDENZIALE

Provider ECM e SEGRETERIA ORGANIZZATIVA
EXPO POINT CONGRESSI EVENTI

INFO www.expopoint.it



meets

GUARD CONSORTIUM




necchi.andrea@hsr.it

@AndreaNecchi



UniSR
Università Vita-Salute San Raffaele

I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato