VIGO NORTE INTERNATIONAL GU DEBATES

CLINICAL VIGNETTE

Muscle-invasive bladder cancer: approaching a classic disease in a new era

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Medical Oncology Department · Centro Integral Oncológico Clara Campal HM CIOCC, Madrid

Patient background

62-year-old

- Never smoker
- Hypothyroidism



Breast cancer (2023-2025)

- **Infiltrating** lobular carcinoma · G1 · **pT2 pN2a M0** · **Lum A**
- Right radical mastectomy + lymphadenectomy
- Adjuvant **Doxorubicin–Cyclophosphamide ×4c → Paclitaxel ×12c**
- Radiotherapy · **Letrozole** + **Abemaciclib** (from 03/2024)

AI-generated image

Jun/25

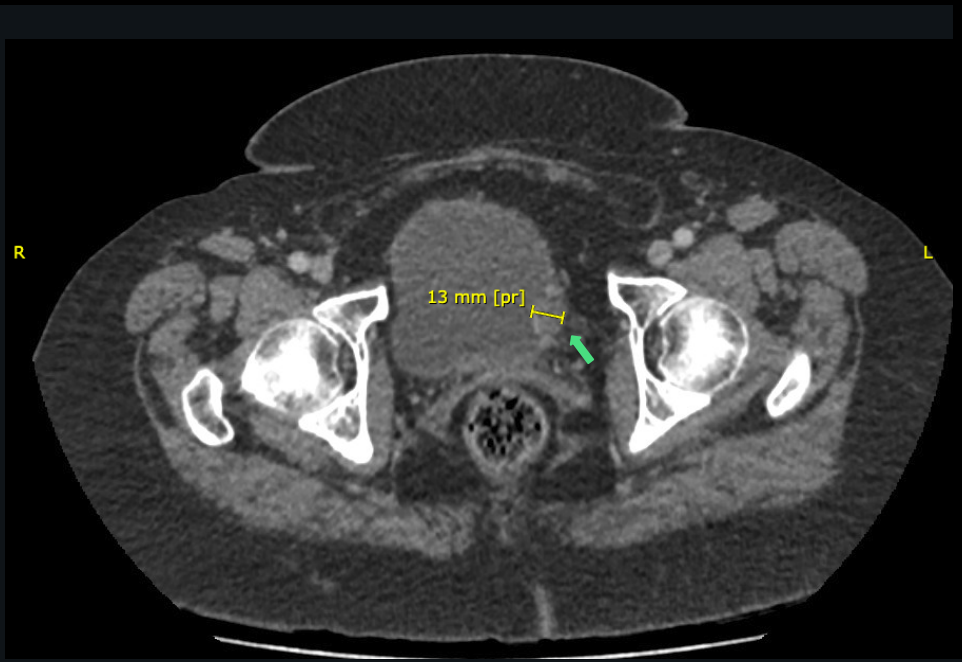
Gross Hematuria during breast-cancer follow-up

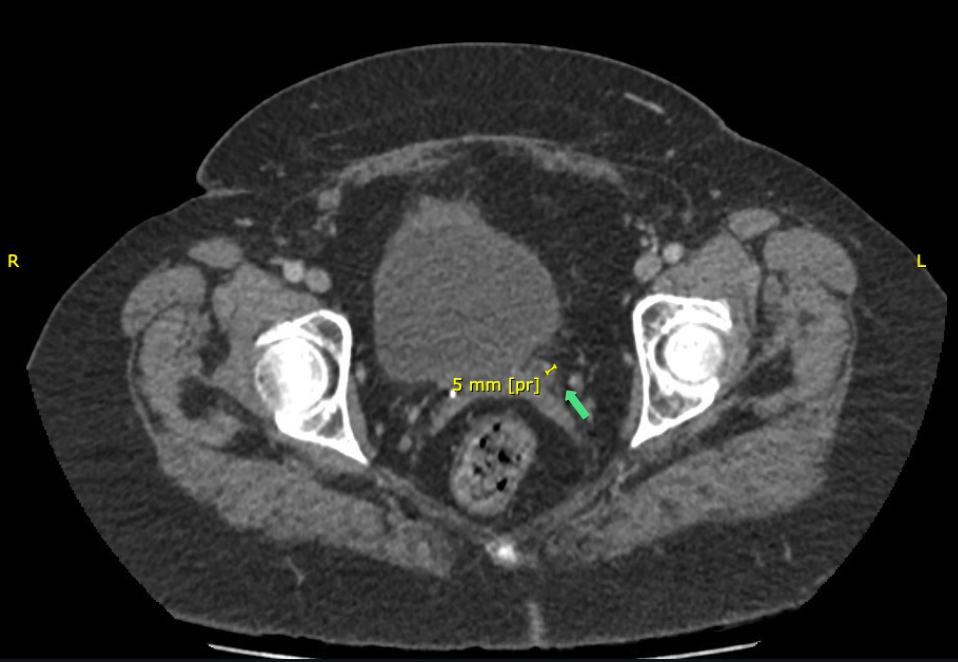
Urine cytology ×2
Both **negative**



Basal urothelial cells in a monolayer with uniform round, pale nuclei and high N:C ratios. Contributed by Maria Cecilia D. Reyes, M.D.

Staging CT scan 16/09/2025





- Focal thickening of the **left posterolateral bladder wall, max 13 mm**, involving the ureteral meatus
- Small focal thickening of the pelvic ureter **5 mm**, proximal to the VUJ

20/08/2025





Susanibarmd, 2017

Pathology (TURBT)

- **Left bladder base**
- Infiltrating **urothelial carcinoma**
- **G3**
- **Squamous differentiation**: **5%**
- **Lymphatic** and/or **vascular** invasion: **doubtful**
- **Associated carcinoma in situ**
- pTNM (8th ed.): **G3pT2**

62-year-old woman

G3 pT2 urothelial carcinoma with 5% squamous component

Prior breast cancer

Treated with cyclophosphamide, doxorubicin and paclitaxel

Abemaciclib discontinued, agreed with the Breast Unit

ECOG 0

CrCl 70 ml/min
Cr 0.68 mg/dl

No neuropathy
No hearing loss
No cardiopaty

What perioperative treatment would be your first option ?

A Cisplatin–gemcitabine

B Cisplatin–gemcitabine–durvalumab (NIAGARA)

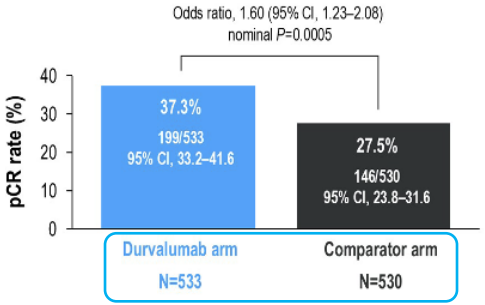
C Enfortumab vedotin + Pembrolizumab KEYNOTE B15/EV-304

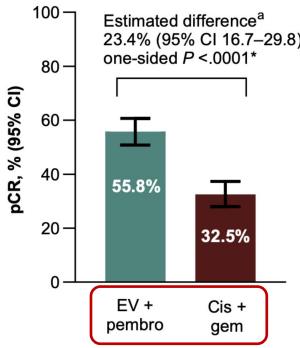
D Surgery

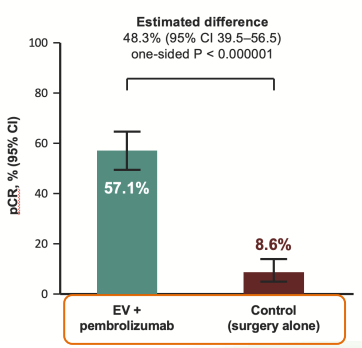
EFS: event-free survival; OS: overall survival; pCR: pathological complete response;
EV-P: Enfortumab Vedotin + Pembrolizumab; GC: Gemcitabine–Cisplatin

Perioperative landscape: what we know in 2026?

Trial	Population	Regimen	Survival	PFS/EFS HR	OS HR	pCR
VESPER	Cisplatin-Eligible	ddMVAC vs GC	3 yr PFS 64% vs 56%	0.77 (0.57–1.02)	0.77 ITT · 0.71 neoadjuvant	**42%** vs 36% (p = 0.2)
NIAGARA	Cisplatin-Eligible	GC + Durvalumab vs GC	—	0.68	0.75	**37.3%** vs 27.5%
KEYNOTE-B15/EV-304	Cisplatin-Eligible	EV-P vs GC	2-year EFS 79.4% vs 66.2%	0.53	0.65	**55.8%** vs 32.5%
KEYNOTE-905/EV-303	Cisplatin-Ineligible	EV-P vs Surgery Alone	2-year EFS 74.7% vs 39.4%	0.40	0.50	**57.1%** vs 8.6%







Pfister C, et al. Eur Urol 2021 · J Clin Oncol 2022 · Lancet Oncol 2024, Powles T, et al. N Engl J Med 2024;391:1773-86. Galsky MD, et al. N Engl J Med 2026;395:338-48. Vulsteke C, et al. N Engl J Med 2026;394:1257-69.

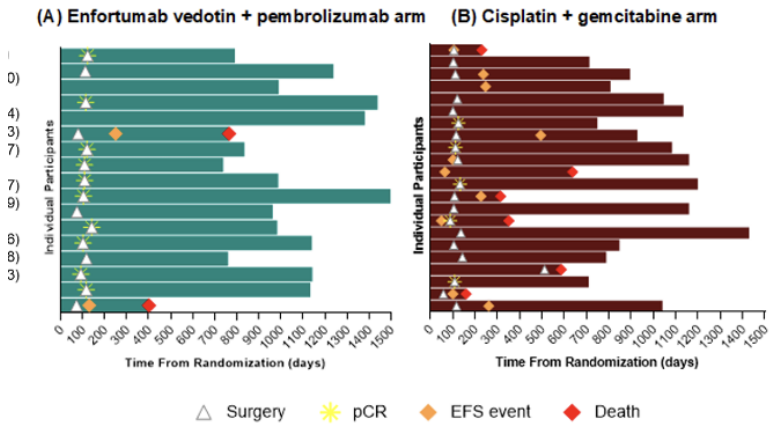
Does a minor squamous component change the plan?

Proportion of non-conventional component in the tumor

Our patient: 5% | **≥50%**: excluded from EV-P pivotal trials | 100%

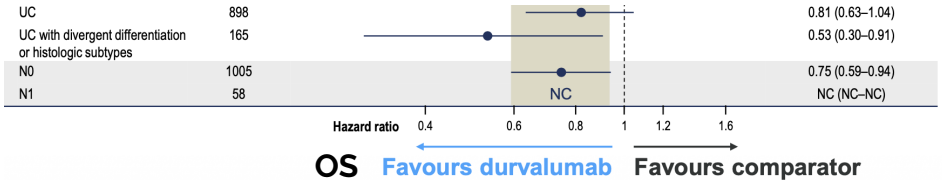
Outcomes for Participants Whose Tumors Have Variant Histology

EV 304 — **UC With Squamous Differentiation** — **4,2%**



NIAGARA

Histology at baseline	Durvalumab N = 533	Comparator N = 530	Total
Urothelial carcinoma	86%	83%	898
UC with subtype / divergent differentiation	14%	17%	165



Take-home: with **5%** squamous differentiation, **managed as conventional urothelial carcinoma**

Timing matters

Our decision **October 2025**

EMA approval

- NIAGARA **(May/25)**
- KN-905 **(Jun/26)*** **Not covered by the spanish NHS**
- KN-B15 **(Positive opinion Sept/26)**

NHS: national health system

Perioperative treatment

Gemcitabine–Cisplatin + Durvalumab



Adverse events

- **Pruritus G1**
- **Grade 1 neuropathy**, lower limbs

Plan

Radical cystectomy → **Adjuvant Durvalumab** (NIAGARA scheme)

Which image would you consider for revaluation after neoadjuvant treatment?

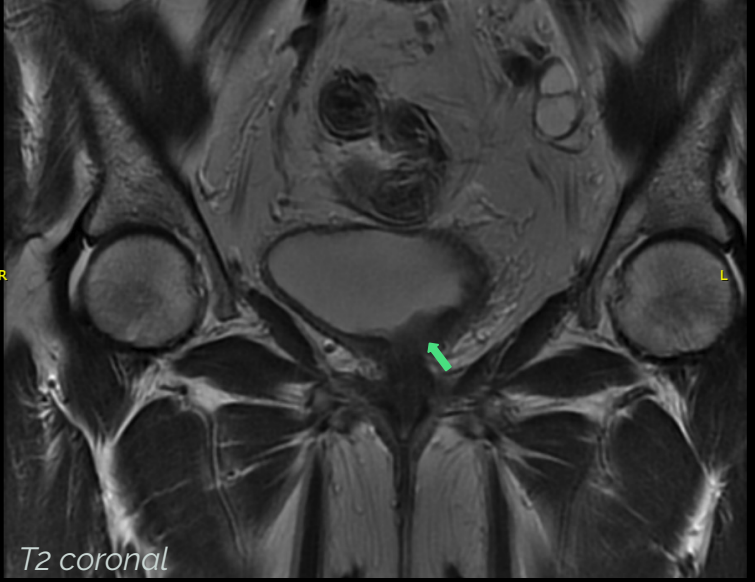
A UroTC

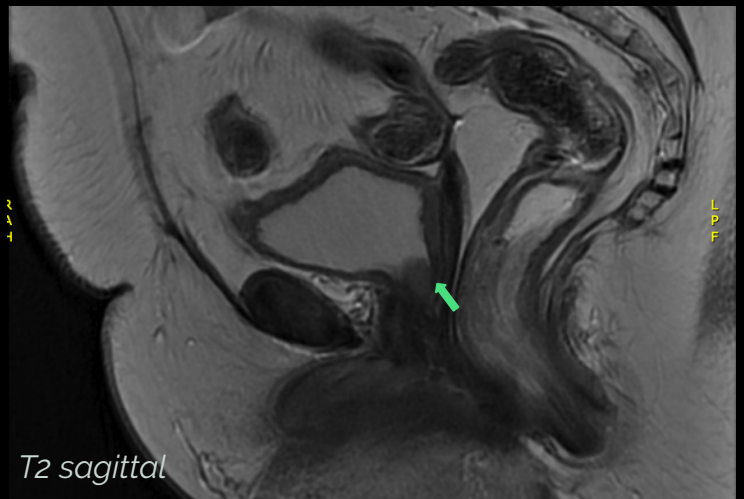
B PET-CT

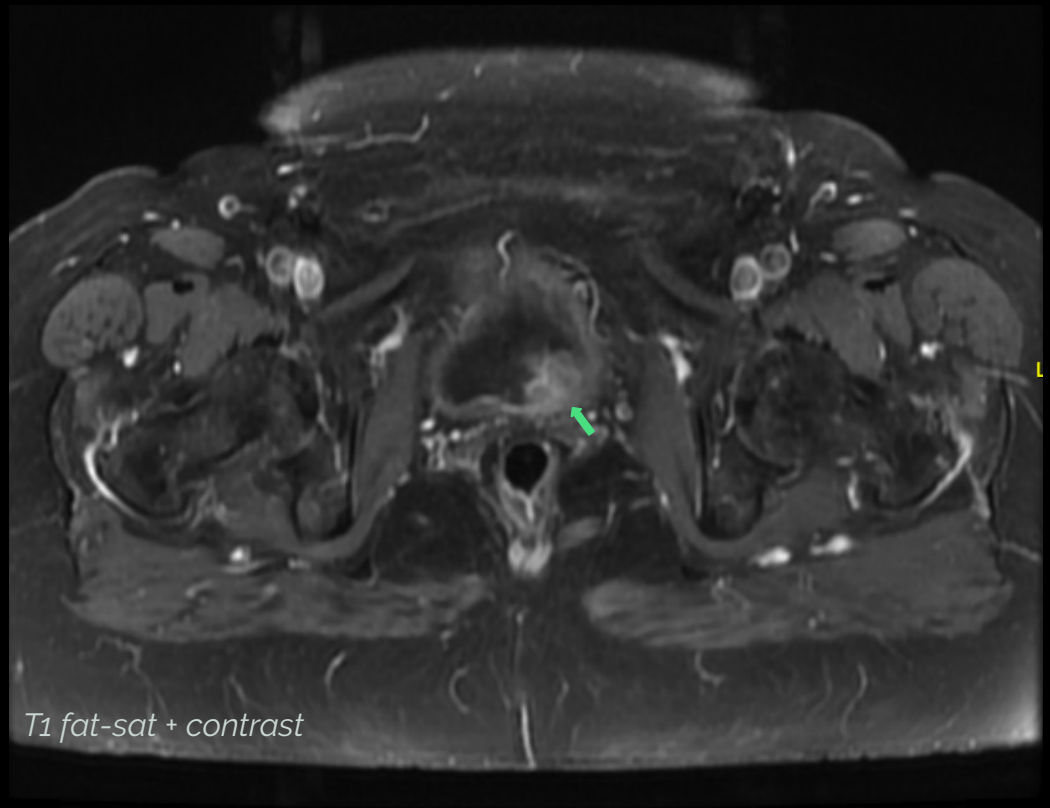
C Pelvic MRI

D Urological ultrasound

Response assessment
Pelvic MRI 16/12/2025







Multiparametric Magnetic Resonance Imaging for Bladder Cancer: Development of VI-RADS

**Valeria Panebianco[a,†,*], Yos
Efstathiou[e], Shaista Hafeez
Montironi[j], Valdair F. Muglia
J. Alfred Witjes[o], Mitsuru Ta**

Panebianco V, et al. Eur

Establish the **risk of muscle invasion** using a 5-point scale derived from three categories:
category
tegory
hanced category

Study	Design	Key Result	What It Adds
Ueno, Eur Urol 2019	Multireader validation, 5 readers	Pooled AUC 0.90 (0.87–0.93) · ICC 0.85	Reproducible between readers
Wang, Radiology 2019	340 tumours, 2 readers	AUC 0.94 for detrusor invasion	**First large validation cohort**
Del Giudice, Eur Urol 2020	Prospective, 231 patients, MRI before TURBT	Sens 91.9% Spec 91.1% · NPV 97.1% · AUC 0.94	In high-risk NMIBC (n = 114), NPV 96.6% to skip re-TURBT
Woo, Eur Urol Oncol 2020	Systematic review and meta-analysis	Pooled sens 0.83 · spec 0.90 · AUC 0.94	**Consistent performance across centres**
Jazayeri, Urol Oncol 2022	Meta-analysis by cutoff	≥3: 89% / 84% ≥4: 77% / 94% (sens / spec)	The **cutoff decides what you optimise**

01/2026

Radical cystectomy

ypT3b pN0 pM0

- **G3** invasive urothelial carcinoma
- **Trigone** involvement
- **Squamous** differentiation (**<5%**)
- **Transmural** infiltration reaching **perivesical soft tissue**
- Associated CIS
- **No downstaging** (cT2 → ypT3b)

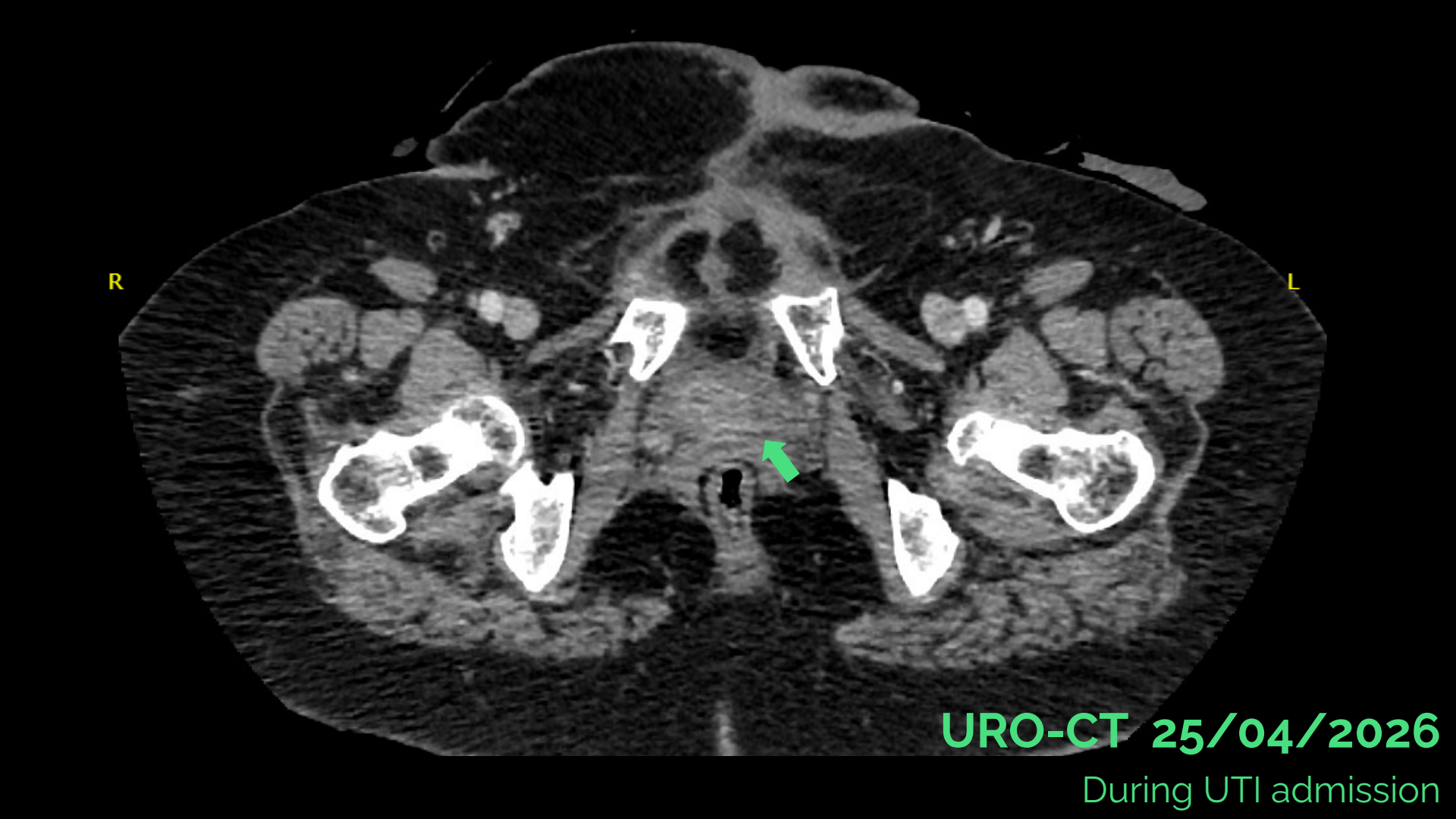
Postoperative course

10/02 – 28/02/2026
Admission for **urinary sepsis** and **acute kidney injury**

03/03/2026
Adjuvant **durvalumab** started (delayed)

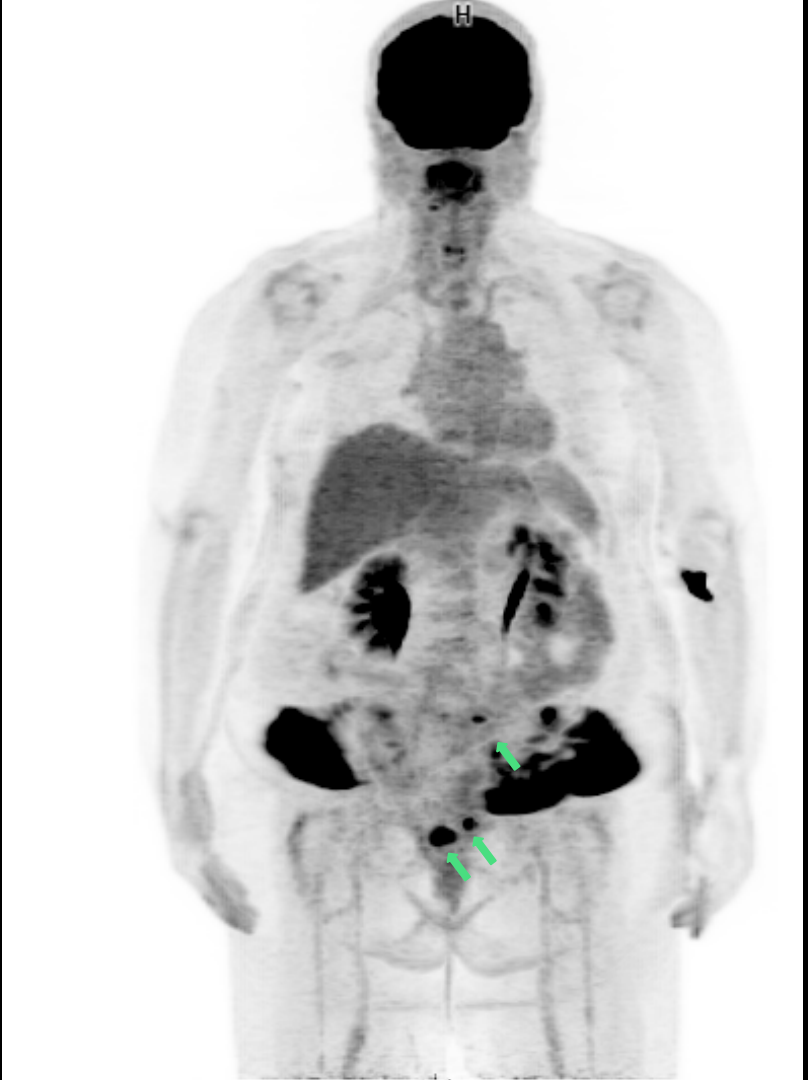
After 3 cycles

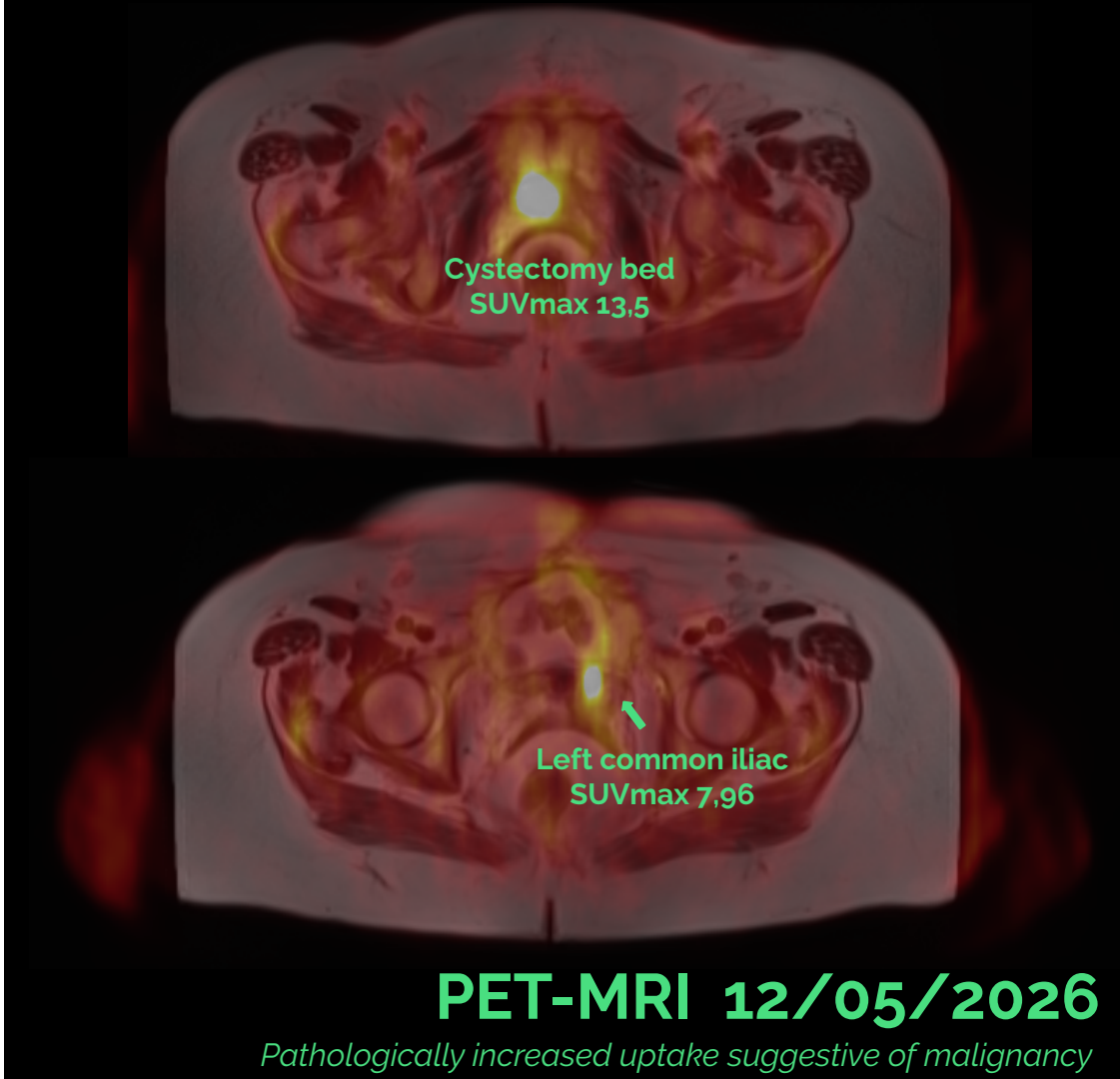
Disease progression
confirmed (25/04/26)



URO-CT 25/04/2026

During UTI admission





PET-MRI 12/05/2026

Pathologically increased uptake suggestive of malignancy

Urothelial carcinoma with 5% squamous component

No tumor downstaging after CIS-GEM-DURVA
Early relapse during adjuvant immunotherapy (3C)

Which treatment would be your first option?

- **A** Salvage surgery
- **B** Local radiotherapy: Tumour bed + LN, continue Durvalumab
- **C** First-line EV-P
- **D** First-line EV

Is there **any biomarker** that would have made you **change your mind?**

Biomarkers in MIBC: what the evidence supports today

Technique	Question It Answers	Best Evidence To Date	Status
PD-L1 (IHC)	Who needs adjuvant immunotherapy?	CheckMate 274 (co-primary met) vs AMBASSADOR (not predictive)	Not a sole determinant
DDR Genes · Molecular Subtyping	Who responds to cisplatin?	SWOG S1314 (OR 3.24); COXEN not predictive; RETAIN-1 endpoint missed	Investigational
Plasma ctDNA After Cystectomy	**Who needs adjuvant immunotherapy?**	IMvigor011: DFS 9.9 vs 4.8 mo; OS 32.8 vs 21.1 mo · TOMBOLA · CheckMate 274	**Predictive · The only level 1 biomarker**
Plasma ctDNA Before Cystectomy	Is the systemic treatment working?	NIAGARA (57→22→9% positive) · Christensen 2019	Prognostic, not for decisions
Urine Tumour DNA	Is there residual disease in the bladder?	NIAGARA: pCR 72% if negative vs 18% if positive · SUNRISE-4	Investigational
MRI (VI-RADS / nacVI-RADS)	Local stage and response	nacVI-RADS NPV 93–98% for residual MI disease; part of the cCR definition	No validated biomarker for cystectomy vs trimodality

Only **plasma ctDNA after cystectomy** currently changes management.
Everything else is prognostic or investigational

Hensley PJ, et al. Nat Rev Urol 2026. doi:10.1038/s41585-026-01179-y

First line: Enfortumab-Vedotin + Pembrolizumab

27/05/2026

EV-P started

C1–C2

Manageable toxicity

- **Rash G2:** Topical and systemic steroids
  Neuropathy G1

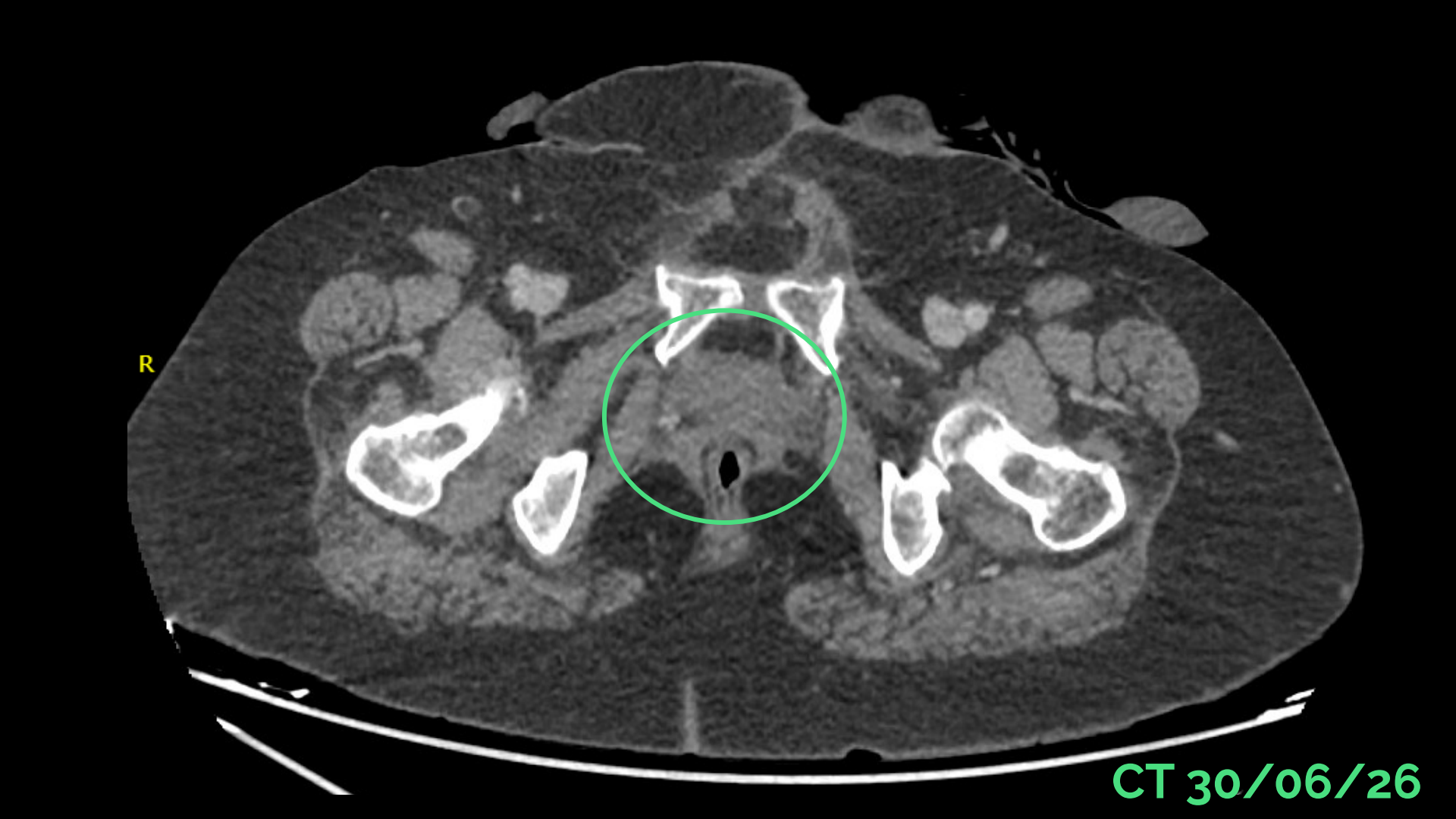
After 2 cycles 30/06/26

Complete response

To date

5 cycles completed

NGS
(BRCA Q2042Q [0,15%])
HER 2 IHC pending


R
CT 30/06/26

Is there any **evidence** of **IO free interval** to consider an **IO rechallange**?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

Outcomes of immune checkpoint inhibitor rechallenge in advanced urothelial carcinoma: results from a global real-world evidence study☆

B. A. Maiorano[1,*], A. Cigliola[1,2], V. Tateo[1], C. Mercinelli[1,2], G. L. Pastorino[2], N. Dizman[3,4], H. Ebrahimi[4], S. K. Pal[4], S. Gupta[5], P. Grivas[6], A. M. Kamat[7], P. E. Spiess[8], N. Agarwal[9] & A. Necchi[1,2]

[1]Department of Medical Oncology, IRCCS San Raffaele Hospital, Milan; [2]Vita-Salute San Raffaele University, Milan, Italy; [3]The University of Texas MD Anderson Cancer Center, Houston; [4]Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte; [5]Taussig Cancer Institute, Cleveland Clinic, Cleveland; [6]University of Washington and Fred Hutchinson Cancer Center, Seattle; [7]MD Anderson Cancer Center, Houston; [8]Moffitt Cancer Center, Tampa; [9]Huntsman Cancer Institute, University of Utah, Salt Lake City, USA

Available online 18 November 2025

Background: Several immune checkpoint inhibitors (ICIs) are approved for urothelial carcinoma (UC), but limited information is currently available regarding the efficacy of rechallenging ICIs in patients with previous ICI exposure.
Patients and methods: A retrospective study was carried out using the TriNetX® database for a large-scale search of patients with advanced UC (aUC) who had received two separate courses of ICIs (either alone or in combinations). Kaplan—Meier analysis was used to estimate progression-free and overall survival (PFS, OS) of ICI rechallenge. Propensity score matching analysis was run to balance and compare groups based on the duration of ICI rechallenge and stage at diagnosis.
Results: Out of 35 789 patients, a cohort of 292 (0.81%) treated with ≥2 ICI-including lines between 2014 and 2024 was identified. There were 86% bladder versus 14% upper tract UC. At initial diagnosis, 49% had stage IV, whereas 51% had stage I-III disease. The median time on prior ICI treatment was 19.5 months; the median time from the end of ICI to the start of ICI rechallenge was 9.4 months. After a median follow-up of 21.7 months, the median OS of ICI rechallenge was 20.5 months, the median PFS was 10.3 months. Previous use of an ICI in a nonmetastatic setting was associated with longer median OS than both lines given in aUC ($P < 0.001$). Among those who received a previous ICI in a metastatic setting, a cut-off of 12 months for the ICI rechallenge was associated with a longer median OS ($P = 0.027$). The longest duration of rechallenge treatment was achieved with anti-programmed cell death protein 1 given after anti-programmed death-ligand 1 therapy (18.2 months, $P < 0.001$).
Conclusions: Although it is an uncommon and not standard strategy, previous ICI in nonmetastatic UC and a period of ≥12 months after previous ICI in the metastatic setting were associated with better outcomes after ICI rechallenge in patients with aUC.
Key words: bladder cancer, first-line therapy, immune checkpoint inhibitors, real-world data, immunotherapy rechallenge

- Rechallenge OS: **20.5 months**.
- PFS: **10.3 months**.
- Prior ICI in a **non-metastatic** setting: longer OS than both lines in advanced disease (p < 0.001).

Original Study

Check for updates

Treatment Rechallenge With Immune Checkpoint Inhibitors in Advanced Urothelial Carcinoma

Dimitrios Makrakis,[1,#] Dimitra Rafailia Bakaloudi,[1,#] Rafee Talukder,[1,#] Genevieve Ihsiu Lin,[2] Leonidas N. Diamantopoulos,[3] Tanya Jindal,[4] Naomi Vather-Wu,[5] Yousef Zakharia,[6] Nishita Tripathi,[7] Neeraj Agarwal,[7] Scott Dawsey,[8] Shilpa Gupta,[8] Eric Lu,[9] Alexandra Drakaki,[9] Sandy Liu,[9] Roubini Zakopoulou,[10] Aristotelis Bamias,[10] Claudia-Maria Fulgenzi,[11,12] Alessio Cortellini,[11,13] David Pinato,[11,14] Pedro Barata,[15,16] Petros Grivas,[1,17,$] Ali Raza Khaki,[18,$] Vadim S. Koshkin[19,$]

Abstract

Immune checkpoint inhibitors (ICI) improve outcomes in patients with advanced urothelial carcinoma (aUC). However, most patients may not respond and develop progressive disease, while toxicity can be an issue. ICI therapy remains a questionable consideration for rechallenge after other therapies are used. Our study described characteristics and treatment response in patients with aUC who were rechallenged with an ICI-based regimen.

Objectives: To examine patient and disease characteristics, toxicity, and clinical outcomes for patients with advanced urothelial carcinoma (aUC) who are rechallenged with immune checkpoint inhibitor (ICI)-based therapy. **Patients and Methods:** In this retrospective cohort, we included patients treated with ICI for aUC after having prior ICI treatment. Endpoints included the evaluation of radiographic response and disease control rates with first and second ICI courses, outcomes based on whether there was a change in ICI class (anti-PD-1 vs. anti-PD-L1), and assessment of the reasons for ICI discontinuation. **Results:** We identified 25 patients with aUC from 9 institutions who received 2 separate ICI courses. ORR with first ICI and second ICI were 39% and 13%, respectively. Most patients discontinued first ICI due to progression (n = 19) or treatment-related toxicity (n = 4). Thirteen patients received non-ICI treatment between the first and second ICI, and 12 patients changed ICI class (anti-PD-1 vs. anti-PD-L1) at rechallenge. Among 10 patients

ORR: **39%** with the first ICI vs. **13%** with the second ICI (rechallenge)

frontiers in Oncology

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Check for updates

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Advancing immune checkpoint inhibitor rechallenge: key insights into efficacy, safety, and personalized strategies in advanced solid tumors

Shifen Lu and Zhong Xie*

Department of Oncology, Oncology Hospital, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, China

Introduction: Immune checkpoint inhibitors (ICIs) have turned out to be a potent treatment of advanced solid tumor, but the issue of therapy discontinuation under the influence of the resistance, or immune-related adverse events (irAEs) is still a significant challenge. ICI rechallenge, which is a reintroduction of immunotherapy after initial failure is a favorable alternative whose guidelines are not standardized.
Methods: This narrative review was a literature synthesis of the existing evidence drawn from PubMed, Web of Science, Embase, and Cochrane Library as up to July 21, 2025. We assessed real-world studies, retrospective cohorts, and meta-analyses, which examined patient selection criteria, rechallenge strategies, efficacy results, and safety profile across different types of solid tumors.
Findings: The predictors of successful rechallenge include persistent initial response (progression-free survival ≥6 months), prolonged treatment-free interval (≥6 months), excellent performance status (ECOG-PS ≤1), and complete irAE resolution (Grade ≤1). The outcome of an after toxicity rechallage is superior to after progression (median PFS: 5.1 vs. 2.9 months). There is a better response to a combination of anti-angiogenics, chemotherapy, or radiotherapy strategies. However, the recurrence rate of irAE is 20%-60% and severe initial toxicities can be a reason to discontinue the drug permanently.
Discussion: ICI rechallenge benefits the right patients significantly. We propose a clinical decision model that might assist in integrating both biological and clinical variables to base individualized rechallenge, but the standard set of criteria and possibilities to validate biomarkers remains in urgent need.

8 Discussion and future perspective

This comprehensive review presents the most recent developments in ICI rechallenge in advanced solid tumors, including the selection of patients, therapeutic strategies and efficacy/safety management. Our analysis highlights the fact that patients with a long-lasting first response (PFS_1 > 6 months), long treatment-free interval (TFI > 6 months), and complete resolution of previous irAEs (to grade ≤1) are the best candidates for rechallenge.

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Thank you four your attention

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