Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Clinical Context and Decision-Making Surrounding Early Discontinuation of Adjuvant Immune Checkpoint Inhibitors in Genitourinary Malignancies: A Real-World Cohort Study

Hayato Hoshina
hoshina.hayato@jichi.ac.jp

Jichi Medical University Hospital
Atsushi Yanase
Jichi Medical University Hospital
Masayuki Kurokawa
Jichi Medical University Hospital
Toru Sugihara
Jichi Medical University Hospital
Ei-ichiro Takaoka
Jichi Medical University Hospital
Haruki Kume
the University of Tokyo
Tetsuya Fujimura
Jichi Medical University Hospital

Research Article

Keywords: immune checkpoint inhibitors, adjuvant therapy, renal cell carcinoma, urothelial carcinoma, treatment persistence, treatment discontinuation, shared decision-making

Posted Date: November 13th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11575221/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Clinical Context and Decision-Making Surrounding Early Discontinuation of Adjuvant Immune Checkpoint Inhibitors in Genitourinary Malignancies: A Real-World Cohort Study

Hayato Hoshina[a]*, Atsushi Yanase[a], Masayuki Kurokawa[a], Toru Sugihara[a], Ei-ichiro Takaoka[a], Haruki Kume[b], Tetsuya Fujimura[a]

[a]Department of Urology, Jichi Medical University Hospital, Shimotsuke, Japan

[b]Department of Urology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan

*Address for Correspondence:

Hayato Hoshina

Department of Urology, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

Telephone: +81-285-44-2111; Fax: +81-285-40-6595; Email: hoshina.hayato@jichi.ac.jp

ORCID

Hayato Hoshina: 0009-0009-5067-0241

Acknowledgements

We would like to thank Editage for assistance with English-language editing. The cost of this service was paid by the authors.

Authors' contributions: **Hayato Hoshina**: Conceptualization, Formal Analysis, and Writing - Original Draft. **Atsushi Yanase, Masayuki Kurokawa, Toru Sugihara** and **Ei-ichiro Takaoka**: Data Curation and Writing - Original Draft. **Haruki Kume** and **Tetsuya Fujimura**: Supervision, Writing - Original Draft, and Writing - Review & Editing. All authors agree to be accountable for all aspects of the work and ensure that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abstract

Purpose: Adjuvant immune checkpoint inhibitors (ICIs) are increasingly used for genitourinary malignancies after curative-intent surgery; however, real-world treatment persistence and the circumstances surrounding early discontinuation are unclear. We evaluated treatment completion and the clinical circumstances and decision-making surrounding permanent discontinuation.

Methods: We retrospectively evaluated 39 consecutive patients who were administered adjuvant pembrolizumab for renal cell carcinoma or nivolumab for urothelial carcinoma at a

single center from 2022 to 2025; the data cut-off date was October 8, 2026. The primary outcome was the completion of a planned 1-year treatment among patients with a definitive completion status. The two cohorts were analyzed descriptively without direct comparison.

Results: Of 37 patients with a definitive treatment status, 20 completed planned therapy (54.1%; 95% confidence interval, 36.9–70.5%) and 17 permanently discontinued treatment before completion (45.9%). The remaining two patients (5.1% of 39) were still on treatment at data cut-off. An adverse event was the documented primary reason for discontinuation in 12 of 17 patients (70.6%); 11 of these 12 (91.7%) followed Grade 1–2 events. Patient preference contributed to nine of 17 discontinuations (52.9%) through patient-initiated or shared decision-making. Grade ≥3 adverse events occurred in two patients (5.1%).

Conclusions: In this retrospective cohort, permanent discontinuation of adjuvant ICI therapy was frequently documented in association with low-grade toxicity and with patient preference, whereas Grade ≥3 toxicity was uncommon. Shared decision-making that balances anticipated recurrence-risk reduction against treatment burden represents an important consideration in individualizing adjuvant immunotherapy.

Keywords: immune checkpoint inhibitors; adjuvant therapy; renal cell carcinoma; urothelial carcinoma; treatment persistence; treatment discontinuation; shared decision-making

Introduction

Immune checkpoint inhibitors (ICIs) have substantially improved the management of genitourinary malignancies.[1–3] Beyond their established role in advanced disease, ICIs are now used as adjuvant therapy for patients at high risk of recurrence after curative surgery.[4–8] Adjuvant pembrolizumab is used for high-risk renal cell carcinoma (RCC),[2,9] and nivolumab for high-risk urothelial carcinoma (UC).[1,10,11] For both conditions, treatment is generally planned for up to 1 year after surgery.

Although clinical trials have demonstrated the efficacy and safety of these treatments, it may be challenging to administer them consistently for the planned duration in routine clinical practice.[1,2] Unlike patients receiving systemic therapy for advanced cancer, those receiving adjuvant therapy have no radiographically detectable disease after surgery and receive treatment to reduce recurrence risk rather than control an existing tumor burden. Consequently, treatment-related symptoms, even when classified as mild or moderate according to the Common Terminology Criteria for Adverse Events (CTCAE)[12], may substantially affect patients' willingness to continue therapy. Repeated hospital visits, postoperative recovery, comorbidities, persistent immune-related adverse events (irAEs), and uncertainty about the magnitude of individual benefit may also influence treatment continuation. Thus, decisions regarding treatment initiation, interruption, resumption, and

permanent discontinuation may depend not only on toxicity severity but also on patient preference and shared decision-making.

Real-world data on completion of planned adjuvant ICI therapy, particularly the clinical circumstances surrounding permanent discontinuation before completion, remain limited. We therefore evaluated treatment completion and the clinical circumstances and decision-making surrounding permanent discontinuation of adjuvant pembrolizumab for RCC and nivolumab for UC in routine clinical practice.

Materials and Methods

Study design and setting

We conducted a single-center retrospective cohort study and included patients who underwent curative-intent surgery for RCC or UC at Jichi Medical University Hospital from March 2022 onward and subsequently started postoperative adjuvant pembrolizumab on or before December 31, 2025. Our data cut-off was October 8, 2026. Patients who received pembrolizumab for RCC and those who received nivolumab for UC were evaluated as parallel real-world cohorts. Since the cohorts differed in disease biology, surgical procedures, eligibility criteria, prior treatment, and ICI regimens, the study was not designed to directly compare the groups.

The study protocol was approved by the ethics committee of Jichi Medical University

Hospital on January 23, 2023 (Approval No. A22-023) and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before participation.

Potentially eligible patients were identified by reviewing treatment records of all patients who received postoperative pembrolizumab or nivolumab at our institution during the study period and cross-referencing them with surgical and electronic medical records. We included all consecutive eligible patients during the study period; therefore, no formal sample size calculation was performed.

We included patients who received at least one course of adjuvant pembrolizumab or nivolumab and had no radiographically detectable disease at treatment initiation. The pembrolizumab cohort included patients with high-risk RCC who had undergone radical or partial nephrectomy and met the KEYNOTE-564 criteria for postoperative adjuvant pembrolizumab.[2] The nivolumab cohort included patients with high-risk UC who had undergone radical cystectomy or radical nephroureterectomy and met the CheckMate 274 criteria for postoperative adjuvant nivolumab.[1] We excluded patients who received ICIs for recurrent or metastatic disease.

Treatment and follow-up

Pembrolizumab was administered at 400 mg every 6 weeks and nivolumab at 480 mg every 4

weeks. Treatment was planned for up to 1 year in both cohorts. Treatment could be temporarily interrupted or permanently discontinued because of adverse events (AEs), disease recurrence, clinical deterioration, patient preference, or other clinical considerations. No dose reductions were made; treatment modifications were limited to temporary interruption, permanent discontinuation, or transition to systemic therapy after recurrence.

Before each treatment cycle, patients underwent clinical and biochemical assessments. Imaging follow-up was typically performed every 3–6 months, at the treating physician's discretion. When an irAE was suspected, the treating physician evaluated the patient and arranged referrals to specialists when clinically indicated. Decisions to interrupt, resume, or permanently discontinue treatment were based on clinical assessment and discussion between the patient and treating physician. For the descriptive reporting of recurrence, patients without documented recurrence were censored at the date of their last available disease assessment.

Data collection

Baseline variables included age, sex, American Society of Anesthesiologists Physical Status classification, surgical procedure, pathological stage, lymph node metastasis, and time from surgery to initiation of adjuvant therapy. Disease-specific pathological and treatment characteristics, including receipt of preoperative chemotherapy in the UC cohort, were also collected.

Treatment-related variables included the ICI start date, number of doses, treatment duration, temporary interruptions, treatment resumption, permanent discontinuation, reasons for discontinuation, and treatment status at data cut-off. Data on the severity and management of AEs and disease recurrence were also collected.

Data were initially extracted by one investigator using a standardized data collection form. To reduce classification bias, all cases of permanent treatment discontinuation were independently reviewed by a second urologist, who focused on the primary reason for discontinuation and the decision-making process. Discrepancies or conflicting documentation were resolved by consensus after the original medical records were reviewed, with priority given to documentation closest to the relevant treatment decision.

Outcomes and definitions

The primary outcome was the completion of the planned 1-year postoperative adjuvant therapy course among patients with a definitive completion status. Treatment completion was defined as receipt of the planned number of doses/continuation of treatment for 12 months from the first dose without permanent discontinuation. Patients who were still on treatment at the data cut-off date were classified as “ongoing” and excluded from the treatment completion analysis.

Secondary outcomes were treatment status at the cut-off date, permanent discontinuation before completion, reasons for discontinuation, temporary treatment

interruptions, treatment duration, AEs, recurrence, and death. Permanent discontinuation before completion was defined as permanent cessation of ICI therapy before the planned treatment duration had elapsed. A temporary interruption was defined as a treatment pause followed by resumption of the same ICI.

For each patient who permanently discontinued treatment, the primary reason was classified as disease recurrence, AEs, deterioration in general condition, comorbidities, patient-initiated discontinuation without a documented clinical indication, or "other."

The decision-making process was classified as "physician-initiated," "shared decision-making reflecting the patient's wishes," "patient-initiated discontinuation," or "not clearly documented." Patient preference was a contributing factor when the medical record clearly indicated that the patient requested or agreed to permanent discontinuation after discussion of the expected treatment benefits and burdens. Overlap between the decision-making classification and primary clinical reason for discontinuation was permitted.

Assessment of adverse events, disease recurrence, and survival outcomes

AEs occurring during adjuvant ICI therapy and considered clinically relevant to treatment were identified through retrospective review of the medical records and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. These included suspected immune-related adverse events (irAEs), as well as exacerbation of

pre-existing autoimmune disease when clinically considered related to ICI therapy. Events were summarized as any grade and Grade ≥3. Since patients could experience multiple AEs, the sum across individual categories could exceed the number of affected patients. Documented management included temporary treatment interruption, systemic corticosteroid administration, hormone replacement therapy, hospitalization, and specialist consultation. Recurrence was defined as imaging-confirmed disease recurrence or progression after initiation of adjuvant therapy and was dated at the first radiological examination showing recurrence. It was classified as occurring during treatment or after treatment completion or discontinuation.

Statistical analysis

Categorical variables are presented as counts and percentages and continuous variables as medians with interquartile ranges. The primary treatment completion proportion was calculated among patients with a definitive treatment status at cut-off, and its exact binomial 95% confidence interval (CI) was estimated. Given the limited sample size and substantial clinical heterogeneity between the RCC and UC cohorts, no formal between-cohort comparisons were performed. All analyses were descriptive and hypothesis-generating. Missing data were not imputed; available-case denominators are reported where applicable. Analyses were performed using JMP Pro, version 17 (SAS Institute, Cary, NC, USA).

Disclosure

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with English-language editing, refinement of wording, and organization of the manuscript text. The tool was not used to generate or modify the study data or to perform the primary statistical analyses. All AI-assisted content was critically reviewed, revised, and verified by the authors, who take full responsibility for the final content of the manuscript.

Results

Patient characteristics

The cohort comprised 39 patients: 17 with RCC who received adjuvant pembrolizumab and 22 with UC who received adjuvant nivolumab (Table 1). The median age was 63 years (54–69) in the RCC cohort and 69 years (64–75) in the UC cohort; 11 (64.7%) and 16 (72.7%) patients, respectively, were men.

In the RCC cohort, 15 patients (88.2%) had pathological T3 disease, 14 (82.4%) had clear-cell histology, and none had lymph node metastasis. Regarding surgical procedures, open nephrectomy was performed in three patients, laparoscopic nephrectomy in eight, robot-assisted partial nephrectomy in two, and robot-assisted radical nephrectomy in four. In the UC cohort, 14 patients (63.6%) underwent robot-assisted radical cystectomy and eight (36.4%) underwent nephroureterectomy. Pathological T stages were T2 in seven patients (31.8%), T3

in 10 (45.5%), T4 in four (18.2%), and Tis in one (4.5%); five patients (22.7%) had lymph node metastasis. All patients in the UC cohort had received preoperative chemotherapy. The median interval from surgery to adjuvant ICI initiation was 2 months [1–2] in both cohorts. During follow-up, three patients in the pembrolizumab cohort were transferred to other institutions for continued care and were censored at their last assessment at our institution. One patient in the nivolumab cohort was lost to follow-up after patient-initiated treatment discontinuation; no other patients were lost to follow-up.

Treatment exposure and outcomes

At the cut-off date, 37 of the 39 patients had a definitive treatment status and were included in the primary treatment completion analysis. Of these, 20 completed the planned treatment, corresponding to a primary completion estimate of 54.1% (95% CI, 36.9–70.5%), whereas 17 (45.9%) permanently discontinued treatment before completion (Figure 1 and Table 2). The other two patients (5.1%) were still on treatment at the cut-off date. Under sensitivity analysis in which both ongoing patients were assumed to complete or not complete treatment, the completion proportion would range from 20/39 (51.3%) to 22/39 (56.4%).

In the RCC cohort, eight patients (47.1%) completed treatment, eight (47.1%) permanently discontinued treatment before completion, and one (5.9%) remained on treatment. In the UC cohort, 12 patients (54.5%) completed treatment, nine (40.9%) permanently

discontinued treatment before completion, and one (4.5%) remained on treatment. Median treatment duration was 7 months (3–11) in the RCC and 9 months (4–10) in the UC cohorts. The corresponding median numbers of doses administered were 5 (2–8) and 10 (7–12), respectively. Temporary treatment interruptions occurred in six patients (15.4%): two in the RCC and four in the UC cohorts.

Adverse events

At least one AE was recorded during adjuvant ICI therapy in 35 patients (89.7%): 16 of 17 patients (94.1%) receiving pembrolizumab and 19 of 22 (86.4%) receiving nivolumab (Tables 2 and 3). Grade ≥3 AEs occurred in two patients (5.1% overall), both in the RCC cohort, and comprised one skin reaction and one pneumonitis event.

Skin reactions were the most frequently recorded any-grade events, occurring in 11 patients (64.7%) in the RCC and 15 (68.2%) in the UC cohorts. Gastrointestinal disorders occurred in seven (41.2%) and four (18.2%) patients, respectively, whereas fatigue occurred in four (23.5%) and nine (40.9%), respectively. Endocrine disorders were recorded in two (11.8%) patients in the RCC cohort and six (27.3%) in the UC cohort. Four patients (10.3%) received systemic corticosteroids, and one (2.6%) required hospitalization because of an AE.

Reasons for permanent discontinuation and decision-making

Among the 17 patients who permanently discontinued treatment, the primary reasons were an AE in 12 (70.6%), disease recurrence in four (23.5%), and another reason in one (5.9%) (Table 4). In the RCC cohort, there were six AE-related and two recurrence-related discontinuations. In the UC cohort, there were six AE-related and two recurrence-related discontinuations, as well as one patient-initiated discontinuation. The median time from treatment initiation to permanent discontinuation was 4 months (range, 1–9 months).

Among the 12 AE-related discontinuations, three events were Grade 1, eight were Grade 2, and one was Grade 3; thus, 11 of 12 AE-related discontinuations (91.7%) followed Grade 1–2 events. Management before permanent discontinuation included systemic corticosteroids in four patients, hormone replacement therapy in four, analgesic treatment in two, topical treatment in one, and clinical follow-up only in one. Treatment was not resumed in these patients because of persistent treatment burden in seven patients and safety concerns in five. The discontinuation decision was classified as physician-initiated in eight patients, as shared decision-making in seven, and as patient-initiated in two. Overall, patient preference contributed through patient-initiated or shared decisions in nine of 17 permanent discontinuations before completion (52.9%). Among the 12 AE-related discontinuations, eight (66.7%) were patient-initiated or based on shared decision-making, and four were physician-initiated.

Recurrence and mortality

The median follow-up duration from ICI initiation was 24 months [IQR, 18–40] for the overall cohort, 20 months [IQR, 16.5–38.5] for the RCC cohort, and 25.5 months [IQR, 20.5–41.3] for the UC cohort. By the cut-off date, disease recurrence had been documented in 12 patients (30.8%): four (23.5%) in the RCC cohort and eight (36.4%) in the UC cohort (Figure 1 and Table 2). Recurrence prompted discontinuation of adjuvant treatment in four patients, two in each cohort. Among the four patients with recurrence in the RCC cohort, two experienced recurrences during adjuvant pembrolizumab therapy, whereas the other two developed recurrence after completing the planned 1-year treatment course. Four patients died during follow-up: one (5.9%) in the RCC cohort and three (13.6%) in the UC cohort.

Discussion

We found that permanent discontinuation of adjuvant ICI therapy in routine clinical practice was frequently associated with clinically manageable, predominantly low-grade AEs and was often influenced by patient preference and shared decision-making. Among patients with a definitive treatment status, nearly half discontinued treatment before completion, although severe AEs were uncommon. These findings suggest that treatment persistence in the adjuvant setting cannot be explained by toxicity severity alone and that the clinical context in which AEs occur and patients' perceptions of treatment burden and preferences also influence

decisions on treatment continuation.

Adjuvant immunotherapy presents a clinical context distinct from systemic treatment for advanced disease. Patients who initiate adjuvant ICI therapy have undergone curative-intent surgery and chosen to receive prolonged postoperative systemic treatment despite having no radiographically detectable disease. Notably, clinically manageable toxicities, including endocrine disorders requiring hormone replacement and other low-grade AEs, were documented as the primary reason for discontinuation in a substantial proportion of patients. Since the therapeutic goal is to reduce the risk of recurrence rather than control active disease, the perceived balance between anticipated benefit and current treatment burden may differ substantially from that in the metastatic setting. Consequently, persistent symptoms, repeated hospital visits, postoperative recovery, long-term supportive treatment such as hormone replacement, and broader logistical or financial burdens, which were not assessed in this study, may assume greater importance in treatment continuation decisions, even in the absence of severe toxicity.

These findings underscore the importance of shared decision-making throughout adjuvant ICI therapy.[13–15] Unlike treatment for advanced disease,[16–20] adjuvant immunotherapy aims to reduce recurrence risk in patients without radiographically detectable disease. Therefore, patients and clinicians must continually weigh the anticipated long-term oncological benefit of treatment against its current burden from the patient's perspective. Treatment

continuation decisions should not be based solely on the presence or CTCAE grade of AEs but should incorporate treatment goals, patient values and preferences, and the level of treatment burden considered acceptable by the patient. This approach may be particularly important for persistent but medically manageable toxicities, for which continued treatment may remain clinically feasible while the perceived burden may be substantial. Concurrently, apparently mild AEs may persist or progress, adversely affect quality of life, and potentially have implications for future treatment options should systemic therapy become necessary after recurrence. Therefore, decisions on temporary interruption or permanent discontinuation should emerge from ongoing clinician–patient dialogue that considers both the immediate consequences of continued treatment and implications for subsequent cancer management.[21]

The clinical relevance of these findings may increase as perioperative and adjuvant immunotherapy becomes more widely used across genitourinary malignancies.[1–3] Perioperative strategies such as the NIAGARA regimen are also increasing the number of patients exposed to ICIs with curative intent.[1–3] Integrating the balance between oncological benefit and patient-perceived burden into routine clinical decisions through shared decision-making may help avoid both unnecessary treatment discontinuation and continuation, while supporting individualized treatment strategies that preserve quality of life and maximize the potential benefit of perioperative and adjuvant immunotherapy.

This study has some limitations. First, its single-center retrospective design and

relatively small sample size may limit the generalizability of its findings. Reliance on retrospective medical-record review may have resulted in under-ascertainment of mild AEs and incomplete or inaccurate documentation of patients' preferences and their contribution to shared decision-making, as these were not evaluated using standardized patient-reported outcome measures or structured decision-making instruments. Although all cases of permanent treatment discontinuation were independently reviewed by a second investigator and discrepancies were resolved by consensus to reduce classification bias, this limitation could not be fully removed. Second, the RCC and UC cohorts were evaluated in parallel without direct comparison because of differences in disease biology, surgical management, and treatment regimens. Third, surveillance imaging was not performed according to a fully standardized protocol but at the discretion of the treating physicians, which may have influenced the timing and detection of disease recurrence. Fourth, incomplete follow-up in a small number of patients, including those transferred to other institutions or subsequently lost to follow-up, may have limited the ascertainment of late recurrence and long-term outcomes. Fifth, the relatively short follow-up duration precluded assessment of the long-term oncological impact of permanent treatment discontinuation before completion of planned adjuvant therapy.

Larger prospective multicenter studies that incorporate standardized surveillance protocols, patient-reported outcomes, and structured assessments of shared decision-making are warranted to better define strategies for optimizing treatment continuation and

discontinuation decisions while maintaining patient-centered care in the adjuvant immunotherapy setting.

Treatment persistence during adjuvant ICI therapy reflects not only the occurrence and severity of AEs but also the balance between anticipated oncological benefit and treatment burden. Shared decision-making may therefore be important for individualizing treatment and optimizing overall clinical benefit while preserving quality of life.

Statements and Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Jichi Medical University Hospital and conformed to the principles of the Declaration of Helsinki on January 23, 2023 (Approval No. A22-023). Written informed consent was obtained from all patients before participation.

Consent for publication

N/A

Data availability

The dataset analyzed in this study is available from the corresponding author upon reasonable request. The data are not publicly available because of patient confidentiality and ethical restrictions.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, Bamias A, Lebret T, Shariat SF, Park SH, Ye D, Agerbaek M, Enting D, McDermott R, Gajate P, Peer A, Milowsky MI, Nosov A, Neif Antonio J Jr, Tupikowski K, Toms L, Fischer BS, Qureshi A, Collette S, Unsal-Kacmaz K, Broughton E, Zardavas D, Koon HB, Galsky MD (2021) Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 384:2102-2114. https://doi.org/10.1056/NEJMoa2034442

2. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, Hajek J, Symeonides SN, Lee JL, Sarwar N, Thiery-Vuillemin A, Gross-Goupil M, Mahave M, Haas NB, Sawrycki P, Gurney H, Chevreau C, Melichar B, Kopyltsov E, Alva A, Burke JM, Doshi G, Topart D, Oudard S, Hammers H, Kitamura H, Bedke J, Perini RF, Zhang P, Imai K, Willemann-Rogerio J, Quinn DI, Powles T, KEYNOTE-564 Investigators (2021) Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med 385:683-694. https://doi.org/10.1056/NEJMoa2106391

3. Powles T, Catto JWF, Galsky MD, Al-Ahmadie H, Meeks JJ, Nishiyama H, Vu TQ, Antonuzzo L, Wiechno P, Atduev V, Kann AG, Kim TH, Suárez C, Chang CH, Roghmann F, Özgüroğlu M, Eigl BJ, Oliveira N, Buchler T, Gadot M, Zakharia Y, Armstrong J, Gupta A, Hois S, van der Heijden MS, NIAGARA Investigators (2024)

Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. N Engl J Med 391:1773-1786. https://doi.org/10.1056/NEJMoa2408154

4. Ciccarese C, Occhipinti D, Arduini D, Di Leo D, Neri A, Roca L, Messina G, Troisi P, Pedone RR, Fucile MA, Belletto R, Sardaro V, Ligato C, Ajdhoni R, Caliciotti F, Sighinolfi C, Tagliaferri L, Rocco B, Tortora G, Iacovelli R (2026) Pattern of disease recurrence and outcomes after progression of high-risk renal cell carcinoma (RCC) patients treated with adjuvant immunotherapy. Cancer Immunol Immunother 75:85. https://doi.org/10.1007/s00262-026-04331-0

5. Lopez-Olivo MA, Kachira JJ, Abdel-Wahab N, Pundole X, Aldrich JD, Carey P, Khan M, Geng Y, Pratt G, Suarez-Almazor ME (2024) A systematic review and meta-analysis of observational studies and uncontrolled trials reporting on the use of checkpoint blockers in patients with cancer and pre-existing autoimmune disease. Eur J Cancer 207:114148. https://doi.org/10.1016/j.ejca.2024.114148

6. Grünwald V, Bex A, Rottey S, Suárez C, Procopio G, Velasco G, Melichar B, Bedke J, Pickering L, Fontes-Sousa M, Schmidinger M, Bamias A, Gross-Goupil M, Porta C, Barthélémy P, Escudier B, Albiges L (2025) Current status of adjuvant immunotherapy and relapse management in renal cell carcinoma: Insights from a European Delphi study. Eur J Cancer 225:115569. https://doi.org/10.1016/j.ejca.2025.115569

7. Narita C, Urabe F, Fukuokaya W, Iwatani K, Imai Y, Yasue K, Mori K, Aikawa K, Yanagisawa T, Kimura S, Tashiro K, Tsuzuki S, Yamada Y, Yuen SKK, Teoh JYC, Shimomura T, Yamada H, Furuta A, Miki J, Kimura T, JIKEI-YAYOI Collaborative Group (2024) Site-specific differences of eligibility for adjuvant immunotherapy among urothelial carcinoma patients treated with radical surgery: Results from a multicenter cohort study. Clin Genitourin Cancer 22:102082. https://doi.org/10.1016/j.clgc.2024.102082

8. Menegat ALRS, Menegat BLRS, Braz LDG, Piccoli MVF, Rebelo TG, de Moraes FCA (2026) Neoadjuvant immune checkpoint inhibitors for muscle-invasive urothelial carcinoma: A systematic review and meta-analysis. Immunotherapy 18:139-155. https://doi.org/10.1080/1750743X.2026.2643128

9. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, Hajek J, Chang YH, Lee JL, Sarwar N, Haas NB, Gurney H, Sawrycki P, Mahave M, Gross-Goupil M, Zhang T, Burke JM, Doshi G, Melichar B, Kopyltsov E, Alva A, Oudard S, Topart D, Hammers H, Kitamura H, McDermott DF, Silva A, Winquist E, Cornell J, Elfiky A, Burgents JE, Perini RF, Powles T, KEYNOTE-564 Investigators (2024) Overall survival with adjuvant pembrolizumab in renal-cell carcinoma. N Engl J Med 390:1359-1371. https://doi.org/10.1056/NEJMoa2312695

10. Tomita Y, Kobayashi K, Kimura G, Oya M, Uemura H, Nishiyama H, Galsky MD, Nasroulah F, Collette S, Broughton E, Ünsal-Kaçmaz K, Kamisuki Y, Bajorin DF (2023) Adjuvant nivolumab versus placebo following radical surgery for high-risk muscle-invasive urothelial carcinoma: A subgroup analysis of Japanese patients enrolled in the phase 3 CheckMate 274 trial. Jpn J Clin Oncol 53:16-25. https://doi.org/10.1093/jjco/hyac155

11. Yanagisawa T, Mori K, Matsukawa A, Kawada T, Katayama S, Laukhtina E, Rajwa P, Quhal F, Pradere B, Fukuokaya W, Iwatani K, Afferi L, Marcq G, Mertens LS, Gallioli A, Tully KH, Caño-Velasco J, Subiela JD, Abu-Ghanem Y, Grobet-Jeandin E, Del Giudice F, Pichler R, Teoh JYC, Moschini M, Krajewski W, Miki J, Shariat SF, Kimura T, European Assoc. of Urology–Young Academic Urologists Urothelial Carcinoma Working Group (EAU-YAU) (2025) Adjuvant immune checkpoint inhibitors for muscle-invasive urothelial carcinoma: An updated systematic review, meta-analysis, and network meta-analysis. Target Oncol 20:57-69. https://doi.org/10.1007/s11523-024-01114-4

12. National Cancer Institute (2017) Common terminology criteria for adverse events (CTCAE), version 5.0. United States Department of Health and Human Services. https://dctd.cancer.gov/research/ctep-trials/trial-development. Accessed 26 June 2007

13. Timbrell D, Santhirapala R (2020) Shared decision making in perioperative medicine. Br J Hosp Med (Lond) 81:1-2. https://doi.org/10.12968/hmed.2019.0295

14. Nedbal C, Naik N, Davis N, Madaan S, Tokas T, Cacciamani G, Ventimiglia E, Geraghty RM, Enikeev D, Somani BK (2024) Comprehensive consent in urology using decision aids, leaflets, videos and newer technologies: Empowering patient choice and shared decision-making. Ther Adv Urol 16:17562872241301729. https://doi.org/10.1177/17562872241301729

15. van Balken M, MacLennan S, Montironi R, van Poppel H, Karavitakis M, Tillier C, van Poelgeest-Pomfret ML, Briers E, Meijlink J, Filicevas A, Ungarelli C, Cornes R, Cardone A, Liatsikos E, Caldwell J, Greene R, Daly J, de Santis A, Yared W, Rogers E (2026) Shared decision-making in urology: The SHINE-URO consensus framework. Eur Urol Focus 12:165-167. https://doi.org/10.1016/j.euf.2026.01.008

16. Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, Iyer G, Vulsteke C, Park SH, Shin SJ, Castellano D, Fornarini G, Li JR, Gümüş M, Mar N, Loriot Y, Fléchon A, Duran I, Drakaki A, Narayanan S, Yu X, Gorla S, Homet Moreno B, van der Heijden MS, EV-302 Trial Investigators (2024) Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med 390:875-888. https://doi.org/10.1056/NEJMoa2312117

17. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordoa T, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutcus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK, CLEAR Trial Investigators (2021) Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 384:1289-1300. https://doi.org/10.1056/NEJMoa2035716

18. Motzer RJ, Rini BI, McDermott DF, Arén Frontera O, Hammers HJ, Carducci MA, Salman P, Escudier B, Beuselinck B, Amin A, Porta C, George S, Neiman V, Bracarda S, Tykodi SS, Barthélémy P, Leibowitz-Amit R, Plimack ER, Oosting SF, Redman B, Melichar B, Powles T, Nathan P, Oudard S, Pook D, Choueiri TK, Donskov F, Grimm MO, Gurney H, Heng DYC, Kollmannsberger CK, Harrison MR, Tomita Y, Duran I, Grünwald V, McHenry MB, Mekan S, Tannir NM, CheckMate 214 investigators (2019) Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: Extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol 20:1370-1385. https://doi.org/10.1016/S1470-2045(19)30413-9

19. Motzer RJ, Powles T, Burotto M, Escudier B, Bourlon MT, Shah AY, Suárez C, Hamzaj A, Porta C, Hocking CM, Kessler ER, Gurney H, Tomita Y, Bedke J, Zhang J, Simsek B, Scheffold C, Apolo AB, Choueiri TK (2022) Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): Long-term follow-up results from an open-label, randomised, phase 3 trial. Lancet Oncol 23:888-898. https://doi.org/10.1016/S1470-2045(22)00290-X

20. Yanagisawa T, Mori K, Kawada T, Katayama S, Tsujino T, Maenosono R, Toyoda S, Nukaya T, Morinaka H, Tamura K, Fukuokaya W, Urabe F, Murakami M, Bekku K, Takahara K, Fujita K, Azuma H, Araki M, Inamoto T, Komura K, Kimura T, JK-FOOT study group (2026) A real-world comparison of nivolumab plus cabozantinib and pembrolizumab plus lenvatinib focusing on safety outcomes in metastatic renal cell carcinoma: Results from the JK-FOOT consortium. Cancer Immunol Immunother 75:84. https://doi.org/10.1007/s00262-025-04288-6

21. Pekala KR, Shill DK, Austria M, Langford AT, Loeb S, Carlsson SV (2024) Shared decision-making before prostate cancer screening decisions. Nat Rev Urol 21:329-338. https://doi.org/10.1038/s41585-023-00840-0

Figure

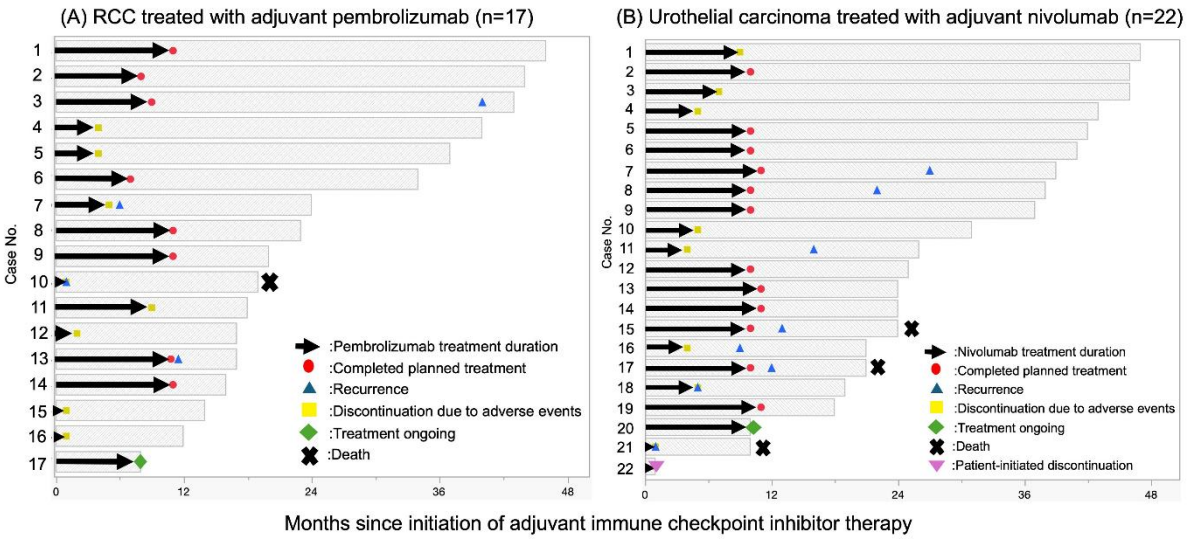


Fig. 1 Individual treatment courses and clinical outcomes during adjuvant immune checkpoint inhibitor therapy

Swimmer plots of patients with (a) renal cell carcinoma who received adjuvant pembrolizumab and (b) urothelial carcinoma who received adjuvant nivolumab. The horizontal axis shows months since initiation of adjuvant therapy. Hatched horizontal bars show follow-up from treatment initiation to the last clinical assessment or death, whereas black arrows show the duration of pembrolizumab or nivolumab treatment. Red circles denote completion of the planned treatment course; blue triangles, disease recurrence; yellow squares, permanent treatment discontinuation because of adverse events; green diamonds, ongoing treatment at data cut-off; black crosses, death; and the magenta inverted triangle, patient-initiated

permanent treatment discontinuation. AE, adverse event; ICI, immune checkpoint inhibitor; RCC, renal cell carcinoma.

Tables

Table 1. Characteristics of the RCC and UC cohorts

	n (%), or median [IQR]	
	RCC cohort	UC cohort
	n=17	*n*=22
Sex, men, n	11 (64.7)	16 (72.7)
Age, years	63 [54–69]	69 [64–75]
ASA-PS, *n*		
1	4 (23.5)	0 (0)
2	12 (70.6)	22 (100)
3	1 (5.9)	0 (0)
Surgical procedure, n		
Open nephrectomy	3 (17.6)	
Laparoscopic nephrectomy	8 (47.1)	
Robot-assisted partial nephrectomy	2 (11.8)	
Robot-assisted radical nephrectomy	4 (23.5)	
Open nephroureterectomy		2 (9.1)
Laparoscopic nephroureterectomy		4 (18.2)

Robot-assisted radical nephroureterectomy		2 (9.1)
Robot-assisted radical cystectomy		14 (63.6)
Pathological T stage, *n*		
T2	2 (11.8)	7 (31.8)
T3	15 (88.2)	10 (45.5)
T4	0	4 (18.2)
Tis	0	1 (4.5)
Histology, *n*		
Clear cell	14 (82.4)	
Non-clear cell	3 (17.6)	
Urothelial carcinoma		22 (100)
Lymph node metastasis, *n*	0 (0)	5 (22.7)
Previous preoperative chemotherapy, *n*	0 (0)	22 (100)
Surgery-to-ICI interval, months	2 [1–2]	2 [1–2]
Number of doses, *n*	5 [2–8]	10 [7–12]

RCC, Renal cell carcinoma; UC, Urothelial carcinoma; IQR, interquartile range;

ASA-PS, American Society of Anesthesiologists Physical Status; ICI, Immune checkpoint

inhibitor

Table 2. Treatment course and clinical outcomes in the RCC and UC cohorts

	(%) or [IQR]		
	Overall	RCC cohort	UC cohort
	n=39	*n*=17	*n*=22
Completed planned treatment, *n*	20 (51.3)	8 (47.1)	12 (54.5)
Permanently discontinued early, *n*	17 (43.6)	8 (47.1)	9 (40.9)
Ongoing at data cutoff, *n*	2 (5.1)	1 (5.9)	1 (4.5)
AE-related discontinuation, *n*	12 (30.8)	6 (35.3)	6 (27.3)
Recurrence-related discontinuation, *n*	4 (10.3)	2 (11.8)	2 (9.1)
Other reason for discontinuation, *n*	1 (2.6)	0 (0)	1 (4.5)
Treatment duration, months	9 [5–10]	7 [3–11]	9 [4–10]
Temporary interruption, *n*	6 (15.4)	2 (11.8)	4 (18.2)
Any-grade AE, *n*	35 (89.7)	16 (94.1)	19 (86.4)
Grade ≥3 AE, *n*	2 (5.1)	2 (11.8)	0 (0)
Systemic corticosteroid use, *n*	4 (10.3)	2 (11.8)	2 (9.1)
Hospitalization due to AE, *n*	1 (2.6)	1 (5.9)	0 (0)
Follow-up duration, months	24 [18–40]	20 [16.5–38.5]	25.5 [20.5–41.3]
Recurrence, *n*	12 (30.8)	4 (23.5)	8 (36.4)
Death, *n*	4 (10.3)	1 (5.9)	3(13.6)

RCC, Renal cell carcinoma; UC, Urothelial carcinoma; IQR, interquartile range;

AE, adverse event;

Table 3. Adverse events during adjuvant ICI therapy according to CTCAE grade in the RCC and UC cohorts.

	RCC cohort, *n*=17 (%)		UC cohort, *n*=22 (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reaction, *n*	11 (64.7)	1 (5.9)	15 (68.2)	0 (0)
Sensory neuropathy, *n*	2 (11.8)	0 (0)	2 (9.1)	0 (0)
Hypertension, *n*	1 (5.9)	0 (0)	0 (0)	0 (0)
Hyperthyroidism, *n*	1 (5.9)	0 (0)	1 (4.5)	0 (0)
Hypothyroidism, *n*	1 (5.9)	0 (0)	2 (9.1)	0 (0)
Hypopituitarism, *n*	0 (0)	0 (0)	1 (4.5)	0 (0)
Adrenal insufficiency, *n*	1 (5.9)	0 (0)	3 (13.6)	0 (0)

Gastrointestinal disorders, *n*	7 (41.2)	0 (0)	4 (18.2)	0 (0)
Fatigue, *n*	4 (23.5)	0 (0)	9 (40.9)	0 (0)
Pneumonitis, *n*	1 (5.9)	1 (5.9)	2 (9.1)	0 (0)
Arthritis, *n*	3 (17.6)	0 (0)	0 (0)	0 (0)
Infusion reaction, *n*	1 (5.9)	0 (0)	0 (0)	0 (0)

CTCAE, Common Terminology Criteria for Adverse Events; RCC, Renal cell carcinoma; UC, Urothelial carcinoma

Table 4. Reasons for permanent discontinuation before completion and associated decision-making processes in the RCC and UC cohort

Patient No.	Cohort	Month of discontinuation	Primary trigger	CTCAE grade	Management	Reason for non-resumption	Decision process
1	RCC	4	Arthritis	1	Steroid	Safety concern	Physician-initiated
2	RCC	4	Pneumonitis	3	Steroid	Safety concern	Physician-initiated
3	RCC	1	Recurrence	−	Systemic treatment	Treatment transition due to recurrence	Physician-initiated

4	RCC	5	Recurrence	−	Systemic treatment	Treatment transition due to recurrence	Physician-initiated
5	RCC	9	Arthritis	1	Analgesic	Persistent burden	Patient-initiated
6	RCC	2	Hypothyroidism	2	Hormone Replacement	Persistent burden	Shared decision
7	RCC	1	Infusion reaction	2	Clinical follow-up	Safety concern	Shared decision
8	RCC	1	Arthritis (Autoimmune diseases)	2	Analgesic	Persistent burden	Shared decision
9	UC	9	Adrenal insufficiency	2	Hormone Replacement	Persistent burden	Shared decision

10	UC	7	Hypopituitarism	2	Hormone Replacement	Persistent burden	Shared decision
11	UC	5	Skin reaction	1	Topical medication	Persistent burden	Shared decision
12	UC	5	Adrenal insufficiency	2	Hormone Replacement	Persistent burden	Shared decision
13	UC	4	Pneumonitis	2	Steroid	Safety concern	Physician-initiated
14	UC	4	Pneumonitis	2	Steroid	Safety concern	Physician-initiated

15	UC	5	Recurrence	−	Systemic treatment	Treatment transition due to recurrence	Physician-initiated
16	UC	1	Patient-initiated discontinuation with loss to follow-up	−	−	−	Patient-initiated
17	UC	1	Recurrence	−	Systemic treatment	Treatment transition due to recurrence	Physician-initiated

RCC, Renal cell carcinoma; UC, Urothelial carcinoma; CTCAE, Common Terminology Criteria for Adverse Events