



Real-world benchmarks for metastatic urothelial carcinoma: a single-center analysis of two standard immunotherapy pathways in Romania

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Abstract

Aim. To establish a real-world benchmark for treatment with the immune checkpoint inhibitors (ICI) and clinical outcomes for patients with metastatic urothelial carcinoma (mUC) by analyzing two distinct, standard-of-care therapeutic sequences at a single Romanian tertiary care center.

Methods. We conducted a retrospective analysis of 30 patients with mUC treated between January 1, 2020, and April 30, 2025. Patients were analyzed in two clinically distinct cohorts: the Avelumab Maintenance Cohort (N=12), which included platinum-eligible patients who responded to first-line platinum-based chemotherapy (PBC) followed by avelumab maintenance, and the Pembrolizumab Cohort (N=18), consisting of patients who received pembrolizumab therapy following disease progression after PBC. The primary endpoint was time to treatment failure (TTF). Secondary endpoints included overall survival (OS) and the incidence of grade ≥ 3 treatment-related adverse events (TRAEs).

Results. The two cohorts displayed different baseline characteristics and clinical trajectories. The Avelumab Maintenance cohort, selected for chemotherapy-sensitive disease, demonstrated a higher disease control rate (DCR) of 91.7%. The Pembrolizumab cohort, representing a more clinically diverse and challenging population, had a DCR of 55.6%. In the Avelumab cohort, median TTF and median OS were not reached. In the Pembrolizumab cohort, the median TTF was 10.2 months and median OS was 21.8 months. Grade ≥ 3 TRAEs were infrequent, occurring in 1 of 12 patients (8.3%) in the Avelumab cohort and 2 of 18 patients (11.1%) in the Pembrolizumab cohort, with no new safety signals identified.

Conclusion. This single-center study provides a context-specific presentation of mUC treated with ICIs effectiveness and safety in the Romanian healthcare context and highlights the impact of systemic factors, such as national healthcare reimbursement policies, on clinical practice.

Keywords: urinary bladder neoplasms, immune checkpoint inhibitors, avelumab, pembrolizumab, Romania

Background and aims

Bladder cancer (BC) represents a significant global health burden. In 2022, an estimated 614,298 new cases were diagnosed worldwide, making it the 9th most common malignancy, with approximately 220,596 deaths attributed to the disease [1]. In Romania, where a national cancer registry is not yet fully established and comprehensive nationwide data collection faces challenges, GLOBOCAN estimates indicate that BC also represents a considerable challenge, with approximately 4,959 new cases and 1,896 deaths reported in 2022 [1].

Urothelial carcinoma (UC) is the most common histological subtype, accounting for over 90% of all BCs [2]. While localized disease can be managed effectively in most cases, metastatic UC (mUC) has historically been associated with a poor prognosis and limited long-term survival [3].

Historically, the management of mUC has relied on platinum-based chemotherapy as the first-line standard of care globally, offering initial tumor responses but with limited long-term disease control and significant toxicity [4]. In the Romanian healthcare context, the landscape of mUC treatment has encountered additional layers of complexity. The pathway to widespread adoption and accessibility of novel therapeutic agents has often been shaped by national healthcare system dynamics, including the evolution of reimbursement policies and the existing infrastructure for delivering advanced oncological treatments. For instance, immune checkpoint inhibitors (ICI) for mUC became available through the national reimbursement system at different time points: Atezolizumab was reimbursed for second-line (L2) therapy from June 2020 (based on trials like IMvigor210/211 [5,6]) and for first-line (L1) cisplatin-ineligible patients from February 2022. Avelumab, as first-line maintenance therapy, gained reimbursement in June 2022, following the positive results of the JAVELIN Bladder 100 study [7]. Pembrolizumab was reimbursed for second-line use from June 2020 (supported by trials like KEYNOTE-045 [8]) and more recently for first-line indications from February 2025 (e.g., based on KEYNOTE-052 [9] or KEYNOTE-

361/1L [10] combo contexts). More reimbursements are synthesized in table I.

The advent of ICIs has truly marked a paradigm shift in the therapeutic arsenal against mUC [11]. These agents, by unleashing the patient’s own immune system to fight cancer cells, initially demonstrated significant clinical benefits in the second-line setting for patients progressing after platinum-based chemotherapy, and subsequently for cisplatin-ineligible patients in the first-line setting [5,6,8,9]. More recently, ICI-based therapy has evolved further, with maintenance immunotherapy after first-line chemotherapy showing survival advantages [7].

Moreover, this shift paved the way for highly effective combination strategies. The combination of an ICI, pembrolizumab, with an antibody-drug conjugate, enfortumab vedotin (EV), has recently revolutionized the first-line treatment landscape for patients with locally advanced or mUC. Data from pivotal trials have demonstrated unprecedented improvements in overall survival (OS) and progression-free survival (PFS) with pembrolizumab + enfortumab vedotin compared to traditional platinum-based chemotherapy, establishing this combination as a new standard of care for eligible patients [12].

While new combinations are redefining mUC care globally, it is crucial to first benchmark the performance of foundational ICI therapies within specific healthcare systems. In Romania, there is a lack of published data regarding the use of immunotherapy in mUC patients. This knowledge gap impedes the optimization of treatment protocols and the ability to tailor therapies to the unique characteristics of the local patient population. Therefore, this study aims to address this critical unmet need by providing the first detailed analysis of mUC patients treated with immunotherapy at a Romanian tertiary center. We focused on patient characteristics, treatment responses, survival outcomes, and safety profiles to provide valuable evidence that can inform clinical practice, guide future research, and help bridge the gap between local oncology practice and international standards.

Table I. Reimbursement timeline and key registration trials of selected immunotherapy agents for metastatic urothelial carcinoma in Romania.

Drug name	Indication in mUC (Line)	Reimbursement date (Romania)	Key registration study/Trial(s)
Atezolizumab	Second-line (L2)	June 2020	IMvigor210 / IMvigor211 [5,6]
Atezolizumab	First-line (cis-ineligible)	February 2022	IMvigor210 [5]
Avelumab	First-line Maintenance	June 2022	JAVELIN Bladder 100 [7]
Pembrolizumab	Second-line (L2)	June 2020	KEYNOTE-045 [8]
Pembrolizumab	First-line	February 2025	KEYNOTE-052 / KEYNOTE-361 [9,10]

Methods

Study population and setting

This retrospective study was conducted at the Department of Medical Oncology, Municipal Clinical Hospital Cluj-Napoca, a tertiary care referral center in Cluj-Napoca, Romania, and included patients diagnosed with mUC between January 1, 2020 and April 30, 2025. The data cut-off for the study was April 30, 2025. The diagnosis was established based on clinical, imaging, and histopathological data, in accordance with current international guidelines [13]. All patients included in the study had a histologically confirmed diagnosis of urothelial carcinoma of the bladder, most commonly obtained through transurethral resection of the bladder tumor (TURBT). The presence of metastatic disease was documented by imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI), performed either at initial diagnosis or during disease progression.

All patients included in the study had a confirmed urothelial main histology. Inclusion criteria were: age ≥ 18 years and initiation of systemic therapy for metastatic disease with available follow-up data. Patients with incomplete medical records were excluded. No patients in this cohort required chronic corticosteroid therapy.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of Municipal Clinical Hospital Cluj-Napoca (Approval No.4/2025). Given the retrospective nature of the study and the use of de-identified data, a waiver of individual informed consent was granted.

To ensure patient confidentiality, all data were pseudonymized. Direct personal identifiers (such as name, full date of birth, national identification number, and address) were removed from the research dataset and replaced with a unique, non-identifiable study code for each patient. The linkage file connecting the study codes to patient identifiers was stored securely, separately from the analysis dataset, with access strictly limited to authorized study personnel for data verification purposes only, if necessary. All data were analyzed and reported in an aggregated manner to prevent any possibility of individual patient identification.

Data collection

Data were systematically collected through a comprehensive review of electronic medical records and physical patient charts. A standardized data collection form was utilized to extract relevant clinical and pathological information. Variables captured included patient demographics (e.g., age at diagnosis, sex), disease characteristics (e.g., primary tumor site, histology, stage at diagnosis, metastatic sites at baseline), and detailed treatment history (e.g., prior lines of therapy, eligibility for platinum-based chemotherapy, previous neoadjuvant/adjuvant treatments). Immunotherapy regimen specifics were recorded, encompassing the line of therapy, specific agents

(pembrolizumab, atezolizumab, avelumab), combination therapies, treatment initiation and discontinuation dates, number of cycles, and reasons for cessation. PD-L1 expression testing was not routinely performed in our institution during the study period; therefore, PD-L1 status was not available for any patient and was not included in the analyses. Furthermore, outcome and safety data were documented, covering tumor response (assessed according to RECIST 1.1 criteria [14]), time to treatment failure (TTF), OS, adverse events (including type, grade according to CTCAE v5.0 [15] and their management) and vital status at last contact or study cut-off point.

Treatment and monitoring

Patients were treated and followed-up according to institutional clinical practice. Avelumab was administered as maintenance therapy at a dose of 10 mg/kg intravenously every 2 weeks, in accordance with the approved label and international guidelines. Pembrolizumab was administered at a dose of 200 mg intravenously every 3 weeks, consistent with the approved dosing schedule during the study period.

Radiological assessment of disease status using CT scans was planned every 12 weeks throughout the study period. In routine practice, some scans were performed earlier or later depending on clinical indications, patient condition, or scheduling/logistical constraints. Disease response was documented as complete response, partial response, stable disease, or progressive disease, according to RECIST 1.1 criteria. Platinum-based chemotherapy, typically consisting of cisplatin or carboplatin combined with gemcitabine was administered for a planned 4-cycle course. Patients who achieved at least stable disease following initial chemotherapy were eligible for maintenance immunotherapy with avelumab, in accordance with contemporary treatment guidelines [13]. Alternatively, patients who progressed after first-line treatment were considered for second-line ICIs, most commonly pembrolizumab.

Statistical analysis

All statistical analyses were performed using R statistical software, version 4.4.3 (2025-02-28 ucrt) – “Trophy Case.” [16]. Continuous variables were reported as medians along with their interquartile ranges (IQRs), and group comparisons were performed using either the Student’s t-test or Mann–Whitney U test, depending on the data distribution. Categorical variables were summarized as absolute counts and percentages, and group differences were evaluated using Chi-square or Fisher’s exact test, as appropriate.

OS was defined as the time interval from the initiation of ICI systemic therapy to death from any cause. TTF was selected as the primary endpoint reflecting treatment duration and clinical benefit, and was defined as the period from initiation of systemic therapy to its discontinuation for any reason, including disease progression, unacceptable toxicity, clinical deterioration, or death. Due to the

retrospective study design and potential heterogeneity in imaging intervals, TTF was deemed a more feasible and consistent measure than progression-free survival (PFS). Patients who were alive and still on treatment at the time of analysis were censored.

Kaplan-Meier survival analysis was employed to estimate both OS and TTF. The reverse Kaplan-Meier method was used to calculate median follow-up duration.

Results

Cohort description

A total of 40 patients with locally advanced or mUC were initially evaluated for inclusion. Ten patients were excluded: eight due to loss to follow-up shortly after diagnosis, and two who declined systemic treatment (Figure 1). The final study cohort comprised of 30 patients who initiated ICIs for metastatic disease.

Patient characteristics

The analysis included 30 patients with a histologically confirmed diagnosis of mUC who initiated systemic therapy between January 1, 2020, and April 30, 2025. Baseline characteristics, stratified by cohort, are detailed in table II. The Pembrolizumab cohort had a higher proportion of patients with an ECOG status of 2 and a slightly higher rate of prior radical cystectomy. The median Charlson Comorbidity Index (CCI) was 9 across both groups, reflecting a population with a significant comorbidity burden.

A total of 30 patients who received systemic first-line treatment for metastatic urothelial carcinoma were included in the analysis. Of these, 12 patients (40.0%) presented with de novo metastatic disease, while 18

patients (60.0%) experienced metastatic recurrence or progression following prior locoregional therapy (Table II). The median follow-up time was 28.42 months (IQR 16.6-43.1).

Treatment pathways and response rates are summarized in table III. The Avelumab Maintenance cohort, by definition, consisted of patients who had at least stable disease after first-line platinum-based chemotherapy. The Disease Control Rate (DCR) in this group was 91.7%. In the Pembrolizumab cohort, the DCR was 55.6%. Among the patients included, 2 patients (6.7%) received systemic treatment after ICI discontinuation. One patient received paclitaxel, and one patient received erdafitinib (FGFR tyrosine kinase inhibitor) as third-line therapy. No patients received antibody-drug conjugates following ICI.

Survival outcomes

In the Avelumab Maintenance cohort (Figure 2), the treatment demonstrated significant durability. The median TTF was not reached (NR), with only 6 treatment failure events recorded among the 12 patients. The Kaplan-Meier curve for TTF remained above the 50% threshold throughout the 30-month follow-up period, indicating that the majority of patients in this pre-selected, chemotherapy-sensitive population continued on maintenance therapy for a prolonged duration.

By contrast, the Pembrolizumab cohort (Figure 3), which represents a post-progression population, had a median TTF of 10.2 months, with 12 events recorded. The Kaplan-Meier curve for this group showed a consistent decline, crossing the 50% mark within the first year of initiating second-line therapy.

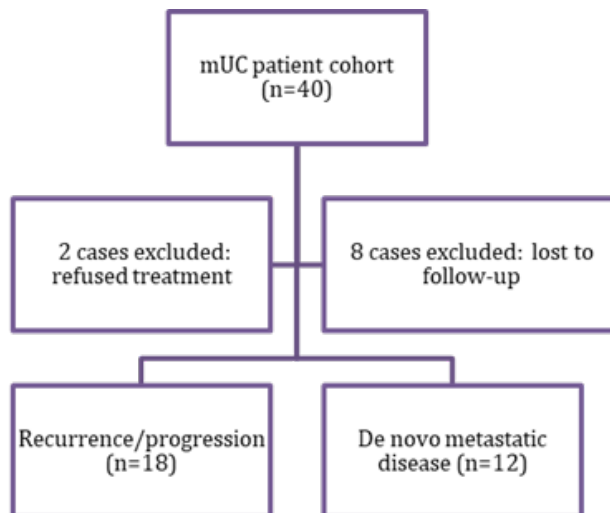


Figure 1. Selection of patients included in the study.

Table II. Baseline Demographics and clinical characteristics by treatment cohort.

Characteristic	Avelumab (N=12)	Pembrolizumab (N=18)
Age [years], median (IQR)	70.5 (67-79.5)	71 (67-79)
Sex, n (%)		
Male	10 (83.3)	14 (77.8)
Female	2 (16.7)	4 (22.2)
ECOG Performance Status, n (%)		
0	4 (33.3)	3 (16.7)
1	8 (66.7)	12 (66.7)
≥2	0	3 (16.7)
CCI, median (IQR)	9 (8-10)	9 (8-10)
Current/Former smoker, n (%)	9 (75.0)	11 (61.1)
Prior Radical Cystectomy, n (%)	4 (33.3%)	11 (61.1%)
Metastatic Setting, n (%)		
De Novo Metastatic	4 (33.3%)	8 (44.4%)
Recurrent/Progressive	8 (66.7%)	10 (55.6%)
Number of metastatic sites, n (%)		
single	4(33.33)	12(66.67)
multiple ≥2	8(66.67)	6(33.33)
Metastatic location, n (%)		
local	1(8.33)	3(16.67)
lymph nodes	6(50)	10(55.56)
bone	6(50)	3(16.67)
lung	6(50)	8(44.44)
liver	3(25)	1(5.56)
intra-abdominal	0	1(5.56)
thigh	0	1(5.56)
Hemoglobin [g/dL], median (IQR)	11.55(10.4;12.35)	12.65(10.58;13)
Creatinine clearance [mL/min/1.73mp], median (IQR)	66.5(41.25;71.75)	73.5(47.25;83)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; IQR, Interquartile Range.

Table III. Treatment characteristics and best response by treatment cohort.

Characteristic	Avelumab Maintenance (N=12)	Pembrolizumab (N=18)
Best Response to IO, n (%)		
Complete Response (CR)	0 (0.0%)	1 (5.6%)
Partial Response (PR)	5 (41.7%)	2 (11.1%)
Stable Disease (SD)	6 (50.0%)	7 (38.9%)
Progressive Disease (PD)	1 (8.3%)	8 (44.4%)
ORR (CR+PR), %	41.7%	16.7%
DCR (CR+PR+SD), %	91.7%	55.6%

Abbreviations: IO, immunotherapy; ORR, objective response rate; DCR, disease control rate.

The analysis of OS, further highlighted the different trajectories of the two cohorts. For the Avelumab Maintenance cohort, the median OS was not reached (NR), with 6 death events observed. The Kaplan-Meier curve is characterized by a distinct plateau, stabilizing at approximately 60% survival beyond the 12-month mark and extending through 30 months of follow-up. This “tail of the curve” is characteristic of effective immunotherapy, suggesting a durable, long-term survival benefit for a subset of patients.

For the Pembrolizumab cohort, the median OS was 21.8 months, with 10 deaths recorded. The Kaplan-Meier curve for this pathway showed a continuous decline over the 48-month follow-up period, with no evidence of a plateau. This pattern indicates a finite survival benefit, consistent with the challenges of treating a more advanced, chemotherapy-refractory patient population.

The very limited use of post-ICI systemic therapy should be considered when interpreting overall survival outcomes in both treatment pathways. In both cohorts,

immune checkpoint inhibition represented the final line of systemic therapy for the vast majority of patients. This finding reflects real-world practice in a reimbursement-

constrained setting and should be taken into account when contextualizing OS results.

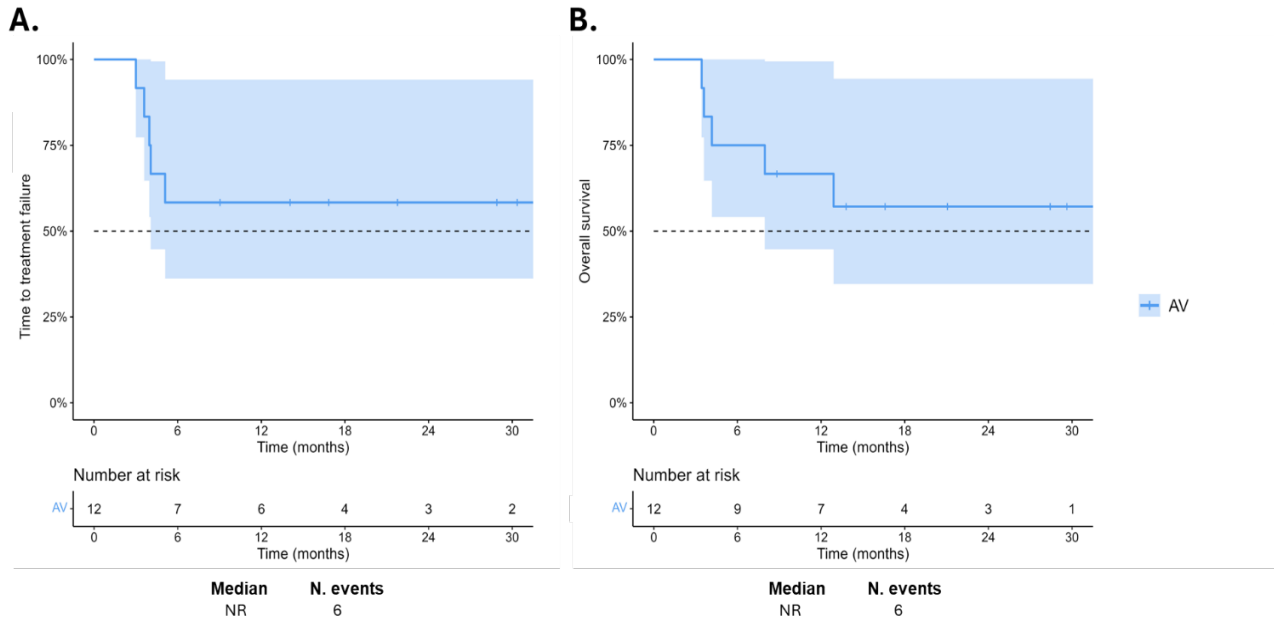


Figure 2. Kaplan-Meier curves for the Avelumab Maintenance Cohort (N=12). AV, avelumab.

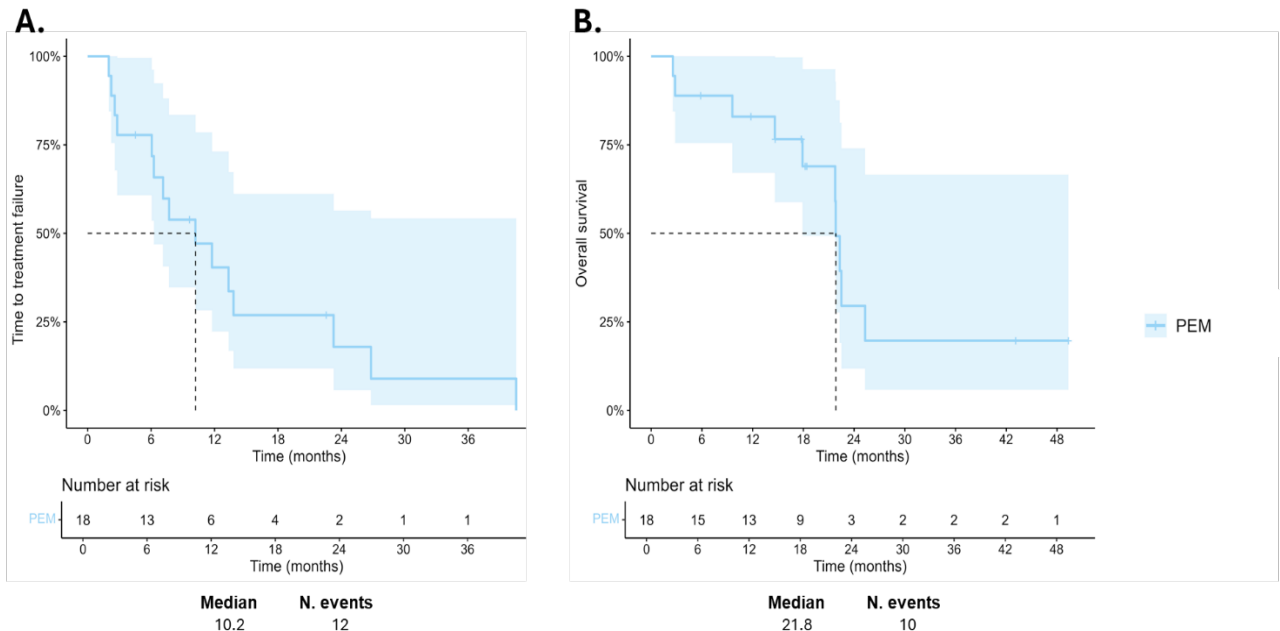


Figure 3. Kaplan-Meier curves for the Pembrolizumab Cohort (N=18). PEM, pembrolizumab.

Table IV. Incidence of treatment-related grade ≥ 3 adverse events.

System Organ Class	Adverse Event	Avelumab (N=12)	Pembrolizumab (N=18)
Gastrointestinal Disorders, n (%)	Diarrhea / Colitis	1 (8.3)	1 (5.6)
Endocrine Disorders, n (%)	Hypothyroidism	0	1 (5.6)

Table V. Detailed presentation of treatment discontinuation reasons.

Reason for discontinuation	Avelumab Maintenance (N=12)	Pembrolizumab (N=18)
Radiologic progression, n (%)	5 (83.3)	9 (75)
Clinical progression, n (%)	1 (16.7)	2 (16.6)
Toxicity, n (%)	0	0
Death, n (%)	0	1 (8.4)
Administrative/access reasons, n (%)	0	0
Patient choice, n (%)	0	0
Other, n (%)	0	0
Total Events, n (%)	6 (100)	12 (100)

Safety and tolerability

The safety profiles were evaluated through the incidence of treatment-related adverse events (TRAEs), graded according to CTCAE v5.0. The overall incidence of Grade ≥ 3 TRAEs was low in both cohorts. Events were reported in 1 of 12 patients (8.3%) in the Avelumab group and 2 of 18 patients (11.1%) in the Pembrolizumab group. The nature of these events was consistent with the known mechanism of action of immune checkpoint inhibitors, and no new safety signals were identified in our cohorts. A summary of Grade ≥ 3 TRAEs is presented in table IV. In addition, lower-grade (Grade 1–2) immune-related adverse events were observed, including fatigue, rash, diarrhea, and endocrine events. All events were generally manageable and did not need permanent discontinuation of therapy.

In the Avelumab cohort, a single Grade 3 TRAE of diarrhea was observed (8.3%). In the Pembrolizumab cohort, two patients experienced Grade 3 events: one with diarrhea/colitis (5.6%) and one with hypothyroidism requiring hospitalization for stabilization (5.6%). All events necessitated the temporary withholding of immunotherapy and initiation of appropriate management (systemic corticosteroids for colitis, hormone replacement for hypothyroidism), in line with standard guidelines. The events resolved, with all patients restarting immunotherapy after the remission of the symptoms. No treatment-related deaths (Grade 5) were observed in either cohort. Detailed reasons for treatment discontinuation are reported in table V.

Discussion

This study presents the first real-world analysis of clinical outcomes for patients with mUC treated with ICI therapy at a single tertiary center in Romania, under current

financial and health insurance constraints. We intentionally present the avelumab-maintenance and post-platinum pembrolizumab pathways separately, because they are not comparable by design: the maintenance pathway consists of platinum-eligible, chemotherapy-sensitive patients who must survive and achieve at least stable disease after first-line platinum, whereas the pembrolizumab pathway represents a post-platinum population with intrinsically less favorable biology and clinical status. Any head-to-head inference across these cohorts would be invalid due to profound selection and survivorship biases. Our purpose is therefore benchmarking, not comparative effectiveness.

Avelumab-maintenance pathway

Within its intended use case, maintenance after disease control with first-line platinum, the avelumab cohort showed durable disease control, with both median TTF and median OS not reached over the observed window. The Kaplan-Meier analyses show a clear survival plateau, with approximately 60% of patients remaining alive after 30 months. These patterns are highly consistent with the maintenance paradigm validated by JAVELIN Bladder 100 [7], where continuing immunologic pressure after chemotherapy-induced tumor debulking prolongs disease control and survival measured from ICI initiation in appropriately selected patients. Our findings confirm that the significant benefits observed in the controlled setting of a clinical trial are achievable in a real-world Romanian patient population. For clinicians and the healthcare system, the take-home message is practical: in Romanian routine care, a substantial fraction of maintenance-eligible patients can expect prolonged time on the platinum plus avelumab pathway, with survival medians extending beyond the current observation window.

The pembrolizumab, platinum refractory pathway

In the cohort receiving pembrolizumab after progression on platinum, we observed an estimated median TTF of 10.2 months and median OS of 21.8 months. These outcomes are encouraging and align with the established efficacy of this agent as a standard of care, validated in the KEYNOTE-045 trial [8]. The lack of a survival plateau in the OS curve for this cohort is consistent with the more challenging clinical scenario of chemotherapy-refractory disease. From a counseling standpoint, these benchmarks suggest that, in Romanian practice, patients who reach pembrolizumab after platinum can expect approximately 10 months of treatment persistence and a median overall survival of nearly 22 months measured from the initiation of pembrolizumab therapy, recognizing wide inter-patient variability.

The safety profiles observed in both cohorts were favorable and consistent with the known spectrum of immune-related adverse events (irAEs) associated with PD-1/PD-L1 inhibitors, with no new safety issues identified. The incidence of Grade ≥ 3 TRAEs was low, at 8.3% in the avelumab arm and 11.1% in the pembrolizumab arm. Notably, the rate of severe toxicity observed in our real-world cohort appears lower than that reported in some pivotal registration trials for these agents. This discrepancy may be attributable to several factors, including differences in patient selection in a real-world versus trial setting, less stringent monitoring protocols outside of a clinical trial, and potential under-reporting inherent to retrospective data collection. Nevertheless, the favorable safety profile observed here supports the feasibility and tolerability of these immunotherapy pathways in routine Romanian clinical practice. The rare severe events were managed effectively with treatment interruption and appropriate interventions, underscoring the importance of vigilant monitoring even with generally well-tolerated therapies.

Strengths and limitations

The principal strength of this study is its position as the first report on real-world ICI outcomes for mUC from Romania, providing valuable data from an underrepresented region in the literature. By framing our analysis within the national reimbursement context, we offer a unique perspective on how health policy can shape clinical practice and patient cohorts. However, some limitations must be acknowledged. The retrospective, single-center design is inherently susceptible to selection bias and unmeasured confounding factors. The most significant limitation is the small sample size ($n=30$), which constrains the statistical power of our analyses and renders the survival estimates, particularly the median OS, unstable and hypothesis-generating at best. The use of TTF as an endpoint, while pragmatic for a real-world study, is less precise than PFS and combines efficacy and toxicity signals. Finally, the treatment arms were heterogeneous, encompassing

different ICI agents and chemotherapy backbones, as the staggered reimbursement dates previously presented inherently influenced treatment availability during the 2020-2025 period covered by our study.

Conclusion and future directions

This study provides the first real-world benchmarks for the use of immune checkpoint inhibitors in metastatic urothelial carcinoma within the Romanian healthcare system, describing two distinct therapeutic pathways that, by their nature, are not directly comparable. Beyond their immediate clinical relevance, these benchmarks serve as a starting point for measuring progress, guiding treatment planning, and informing policy decisions in a setting where access to novel agents remains uneven.

The findings highlight both the potential for durable disease control in appropriately selected patients and the variability in outcomes shaped by patient biology, treatment sequencing, and system-level factors. They also underscore the importance of interpreting real-world results in the context of each pathway's inherent selection dynamics, rather than through cross-comparison.

Future progress will depend on expanding from single-center observations to coordinated, multicenter, and ideally national data collection efforts. Building a structured registry that integrates clinical, biological, and patient-reported outcomes will enable more precise prognostication, equitable access to innovation, and robust evaluation of new therapies as they become available. Embedding these efforts into routine practice will ensure that benchmarks remain dynamic, reflective of evolving standards, and directly applicable to the realities of health care delivery in Romania.

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Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of the Clinical Municipal Hospital, Cluj-Napoca, Romania, approval number 4/2025, dated March 13, 2025.

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