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Review

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Shining light on immunotherapy in metastatic urothelial carcinoma: trends and prospects

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Abstract

Urothelial carcinoma (UC), particularly in its advanced and metastatic stages, poses major treatment challenges. Platinum-based chemotherapy remains the standard front-line treatment due to its superior initial disease control. However, its long-term efficacy has frequently hampered by chemoresistance. Immune checkpoint inhibitors (ICIs) have transformed the treatment of UC, offering durable responses, particularly in the metastatic urothelial carcinoma (mUC) setting. The strategic integration of ICIs, like avelumab in the first-line maintenance setting following chemotherapy, has significantly improved overall survival, representing a key shift in treatment sequencing. Concurrently, advancements in tumor molecular profile have enabled the development of novel targeted therapies for mUC, including fibroblast growth factor receptor inhibitors, Poly (ADP-ribose) polymerase (PARP) inhibitors, anti-HER2 agents, and antibody–drug conjugates specifically targeting Nectin-4. Furthermore, numerous ongoing clinical trials are actively exploring additional molecular targets and pathways to further enhance treatment options for mUC. This review outlines the evolving therapeutic landscape of mUC, emphasizing the limitations of ICI monotherapy, the promise of maintenance strategies, and the emergence of rational combination regimens for improved patient outcomes. Advances in biomarker-guided approaches, including circulating tumor DNA, tumor mutational burden, and ligand programmed death-1 expression, along with emerging biomarkers, such as T-effector gene signatures, ApolipoproteinB mRNA editing enzyme catalytic (APOBEC) mutagenesis patterns, and tumor microenvironment, are also discussed as essential tools for optimizing personalized treatment in the era of precision immunotherapy.

Keywords: Antibody–drug conjugates, Biomarkers, Clinical trials, Immune checkpoint inhibitors, Immunotherapy, Urothelial carcinoma

1. Introduction

Urothelial carcinoma (UC) arises from the urothelial epithelium, a specialized lining that extends throughout the urinary tract, beginning in the renal calyces and renal pelvis, coursing down the ureters, and continuing through the urinary bladder, urethra, and prostatic urethra.[1] Although UC covers a spectrum of tumors originating from these various anatomical sites, the bladder is far the most commonly affected organ, accounting for over 90% of all urothelial malignancies. As such, UC represents the predominant histopathological subtype of bladder cancer, which is currently ranked as the tenth most frequently diagnosed malignancy globally.[2] The increasing incidence of UC over time highlights its growing impact on public health concerns, with a significant socioeconomic burden.[1–3] Nevertheless, despite progress in systematic medical oncology, outcomes in advanced or metastatic UC (mUC) remain discouraging, with median overall survival (OS) still hovering around 15 months from diagnosis. Past decades witnessed cisplatin-based chemotherapy, particularly gemcitabine plus cisplatin (GC) and methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC), as the first-line palliative treatment for advanced or mUC.[3] While GC and M-VAC both offer comparable OS and time to treatment failure, GC is generally favored due to its lower mucosal and hematological toxicity. Despite achieving an overall response rate (ORR) of approximately 50%, a progression-free survival (PFS) of only 7 months, and an OS of about 13 to 15 months, these chemotherapy regimens generally yield modest benefits.[1,4] The therapeutic window is further constrained by cisplatin ineligibility, affecting nearly half of the mUC population due to factors such as impaired renal function, hearing loss/poor Eastern cooperative oncology group (ECOG) performance status (PS), peripheral neuropathy, old age, or other comorbidities, leading to carboplatin being used as a substitute in these cases. Unfortunately, subsequent treatments after the first-line therapy failure have shown limited success, with conventional cytotoxic agents (monotherapy or in combination) yielding unsatisfactory outcomes. Historically, UC patients have had a median OS with a 5-year survival rate of less than 7%, highlighting the urgent need for more effective therapeutic strategies in advanced or mUC.[5]

Recent phase I–III trials have accelerated the development of novel systemic therapies for UC, with several key results emerging over the past few years.[6–8] At the front-line of this therapeutic evaluation are immune checkpoint inhibitors (ICIs), which

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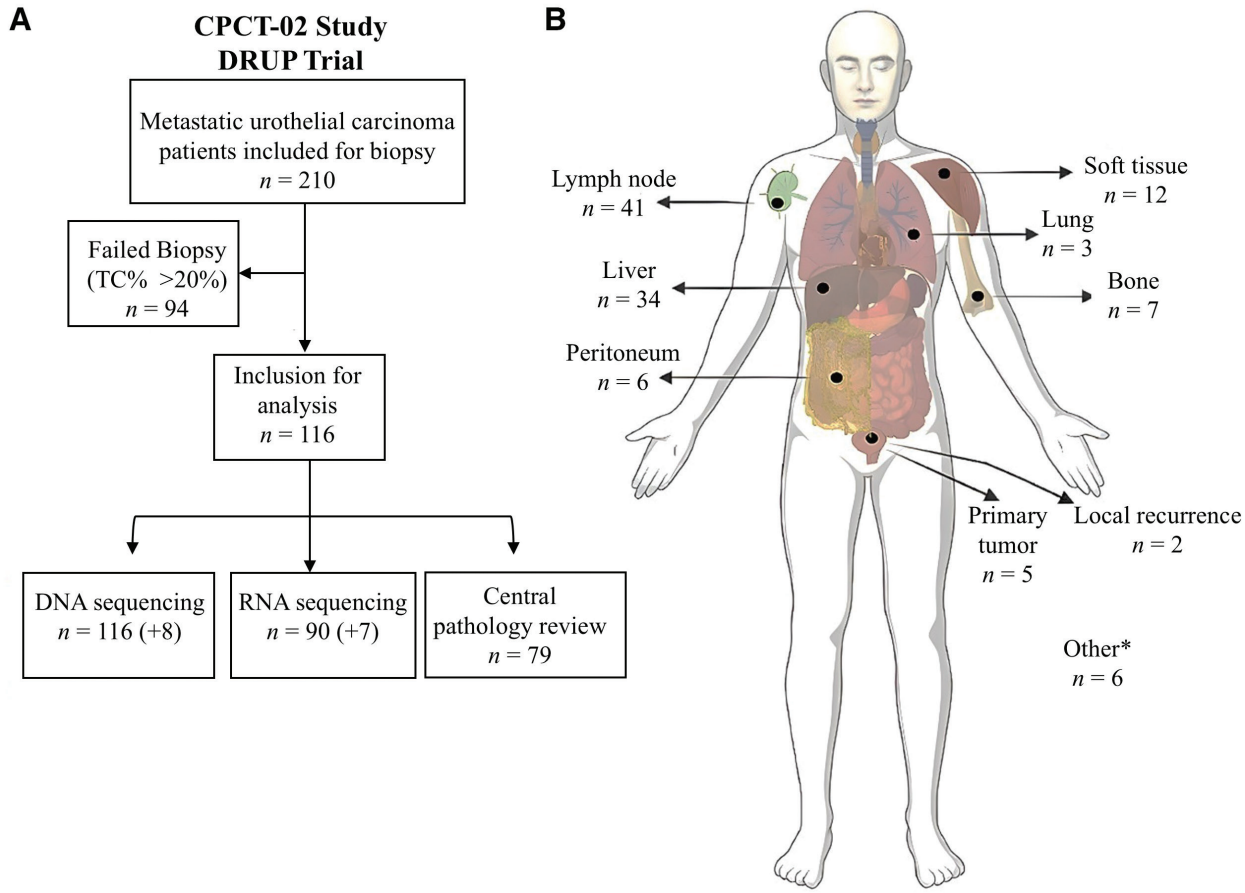

Figure 1. Study design and biopsy site distribution in mUC patients. (A) Flow diagram outlining patient selection. Of 210 individuals with mUC, 116 had tumor samples with ≥20% cellularity for whole-genome sequencing (WGS) and 90 were eligible for RNA sequencing (RNA-seq). Central pathology review was performed for 79 cases (from either the primary tumor or metastatic sites). Repeat biopsies at progression provided additional DNA (n = 8) and RNA (n = 7) samples. (B) Distribution of biopsy sites used for WGS analysis. *"Other" biopsy locations included abdominal/pelvic masses (n = 3), adrenal gland (n = 1), brain (n = 1), and one unspecified location[15]. Copyright 2022, Elsevier B.V.

target regulatory pathways, such as programmed death-1 (PD-1) and its ligand PD-L1 and CLTA-4, to restore antitumor immunity.[9] These agents have demonstrated meaningful clinical activity and are now integrated across multiple lines of treatment in mUC patients after platinum-based chemotherapy. Similarly, precision-targeted therapies, including fibroblast growth factor receptor (FGFR), tyrosine kinase inhibitors, and antibody–drug conjugates (ADCs) directed against antigens such as Nectin-4, have further expanded the armamentarium.[10] Nevertheless, ICIs remain the most transformative class to date and are strongly recommended as forefront treatment options for individuals who are ineligible for platinum-based chemotherapy, especially those demonstrating PD-L1 positivity.[9,11] Notably, avelumab, a PD-L1 inhibitor, has received approval as maintenance therapy for patients who achieve disease control after initial chemotherapy.[12] Although ICIs have demonstrated clinical benefits across various stages of UC, therapeutic challenges remain in terms of primary and acquired resistance, limited efficacy in biomarker-unselected populations, and the lack of reliable predictive biomarkers capable of guiding treatment selection.[13] Tumor-intrinsic mechanisms, such as impaired antigen presentation and activation of oncogenic pathways (e.g., TGF-β, PI3K/AKT), combined with immunosuppressive components of the tumor microenvironment (TME), such as regulatory T cells (Treg), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), contribute to immune evasion.[14] A comprehensive genomic and molecular profiling of mUC (Figure 1) emphasizes the biological complexity and heterogeneity of the disease. Meanwhile, biomarkers including PD-L1, tumor mutational burden (TMB), and circulating tumor DNA (ctDNA) show promise but lack standardization and predictive consistency.[15–17] Emerging biomarkers like T-effector gene signatures, APOBEC mutagenesis, TGF-β signaling, and tumor-infiltrating lymphocyte (TIL) profiles further highlight the need for biomarker-driven and combination-based immunotherapeutic strategies to optimize clinical outcomes and improve treatment efficacy.[17,18]

In this mini-review, we summarize the evolution of ICIs in UC, critically assess emerging resistance mechanisms and biomarker-guided treatment strategies, and highlight novel combination and drug-delivery approaches designed to achieve more durable clinical responses in advanced or mUC.

2. Immunobiology and resistance mechanism in mUC

mUC exhibits a highly immunogenic profile due to its high TMB and frequent neoantigen formation, which theoretically enhances susceptibility to ICIs. Despite these features, durable

responses to ICIs remain limited to a subset of patients, largely due to both tumor-intrinsic and microenvironment-mediated immune evasion mechanisms. The TME in mUC plays a main role in modulating immune responses and promoting immune resistance.[18] It is frequently populated by immunosuppressive cell populations, such as Tregs, MDSCs, and TAMs, which attenuate cytotoxic T-cell activity and hinder the efficacy of immunotherapies. Moreover, antigen presentation is often compromised in mUC through downregulation of major histocompatibility complex (MHC) class-I molecules and mutations in β2-microglobulin, impairing immune recognition and tumor surveillance.[19] Another key feature of the mUC TME is the dysregulation of the TGF-β signaling pathway in stromal fibroblasts, which contributes to promoting immune exclusion by physically preventing T-cell infiltration into the tumor parenchyma, further complicating effective immune surveillance. This immune barrier, combined with chronic exposure to tumor antigens, induces T-cell exhaustion, marked by the upregulation of multiple inhibitory receptors (e.g., LAG-3, TIM-3, TIGIT) that may render PD-1/PD-L1 blockade insufficient.[19,20] These resistance mechanisms highlight the need for biomarker-guided combinatorial approaches to overcome immunotherapy limitations.

To address the aforementioned challenges, integrating ICIs with agents targeting the TME is a promising strategy. Modulating pathways like TGF-β or myeloid suppression or utilizing alternative checkpoints (e.g., LAG-3, TIGIT) may enhance treatment efficacy, as summarized in Table 1. Investigational strategies under exploration include dual checkpoint inhibition (e.g., PD-1 plus CLTA-4, TIGIT, or LAG-3 blockade), TME modulation through TGF-β or adenosine pathway inhibition, and combinations with targeted therapies, ADCs, vaccines, and oncolytic viruses designed to enhance antigen presentation and T-cell recruitment.[10,14,20] These combination therapies hold the potential to overcome the existing barriers in mUC immunotherapy and broaden the scope of patient responses. In this rapidly evolving landscape, a deeper understanding of the biological mechanisms behind the immune resistance is crucial for the rational design of new immunotherapeutic combinations (Table 1). Such strategies may ultimately help broaden and sustain responses in mUC patients, offering more durable and effective treatment outcomes.

3. Comparative evaluation of ICI trials in mUC and real-world data

Over the past decade, multiple phase I–III trials have evaluated ICIs across various treatment lines in mUC; however, meaningful cross-trial comparison remains challenging due to substantial methodological heterogeneity. Variations in trial designs, such as first-line, postplatinum, and maintenance settings, and differences in PD-L1 immunohistochemical assay platforms (e.g., SP142, 22C3, and SP263), cutoff thresholds, eligibility criteria (cisplatin-eligible versus cisplatin-ineligible), and endpoint definitions (RECIST v1.1 versus immune-modified response evoluation critera in solid tumors (RECIST)) contribute to variability in reported outcomes.[22,23] For instance, the IMvigor210 and CheckMate275 trials showed response rates of 15% to 21% using single-arm designs in platinum-refractory disease, whereas the KEYNOTE-045 trial demonstrated an OS benefit for pembrolizumab over chemotherapy in a randomized setting, independent of PD-L1 status.[10,18] In contrast, the IMvigor211 trial failed to meet its primary endpoint, illustrating how differences in PD-L1 scoring methodology and patient selection can influence results.[10] Importantly, the JAVELIN Bladder 100 trial established avelumab as the first-line immunotherapy to improve survival in a switch-maintenance strategy after platinum-based chemotherapy, marking a pivotal shift in the treatment landscape.[24]

While these trial results are essential for advancing mUC therapy, real-world data increasingly provide valuable insights into how therapies perform in broader, more diverse patient populations outside the controlled clinical trial setting. Real-world studies such as READY and AVENANCE, which evaluated avelumab maintenance postchemotherapy, reveal different efficacy and toxicity profiles compared with clinical cohorts, highlighting the importance of assessing the real-world applicability of treatment regimens.[25,26] These data often demonstrate variations in response rates, side-effect profiles, and treatment landscape across heterogeneous mUC patients. To better understand the strengths and limitations of current ICI therapies in mUC, a standardized, biomarker-guided evaluation framework is required. A more nuanced analysis combining data from clinical trials and real-world studies helps to optimize ICI utilization and patient outcomes. Table 2 summarizes key clinical trial features and outcomes, highlighting major limitations, such as selection bias, assay heterogeneity, and small sample sizes, while also indicating that real-world data increasingly reveal divergent toxicity and response patterns compared with those observed in highly selected clinical trial cohorts.[18,26] Moreover, it compares the effectiveness of ICI regimens in controlled trial settings versus broader real-world populations to provide a more balanced perspective of their clinical utility.

Table 1

Resistance mechanisms and emerging combination strategies in mUC.[18–21]

Resistance mechanism	Key groups	Effect on immunity	Potential combination strategy
Loss of antigen presentation	MHC-I, β2-microglobulin mutations	Tumor becomes invisible to T cells	TLR agonists, vaccines, and oncolytic viruses
Immunosuppressive microenvironment	Tregs, MDSCs, TAMs	Suppresses effector T-cell activation	ICI + CSF1R, CXR2, or PI3Kγ inhibitors
T-cell exclusion (stromal barrier)	TGF-β signaling, cancer-associated fibroblast	Impaired T-cell infiltration	PD-1/PD-L1 + TGF-β inhibitors
Oncogenic signaling modules	PI3K/AKT, WNT/β-catenin	Noninflamed cold tumor	ICI-targeted pathway inhibitors (PI3K, WNT, FGFR)
T-cell exhaustion/checkpoint redundancy	LAG-3, TIM-3, TIGIT	Limited response to PD-1 blockades	Dual checkpoint blockade (PD-1 + LAG-3/TIGIT/TIM-3)
Immunometabolism suppression	Adenosine (CD39/CD73), IDO1	Inhibits T-cell function	A2A receptor antagonists, CD73 inhibitors + ICIs

CSF1R, colony stimulating factor 1 receptor.

Table 2

Summary of single-arm phase I/II/III clinical trials of ICIs in mUC, with additional insights from real-world data analysis.

National clinical trial (Clinicaltrials.gov)	Phase	Treatment setting/ population	Intervention	PD-L1 assay/cutoff	ORR (%)	PFS (months)	OS (months)	Key limitations
KEYNOTE-012 (NCT01848834)[10]	I	Any line	Atezolizumab	SP142 (exploratory 27.0)	27.0	2.0 (2.0–4.0)	13.0 (5.0–20.0)	Early-phase heterogeneous population and small cohort
JAVELIN solid tumor (NCT01772004)[24]	Ib	Second line	Avelumab	Dako73-10 (exploratory)	18.2	1.6 (1.5–4.4)	13.7 (8.5–not estimable)	Small cohort, single-arm, and nonrandomized
IMvigor210[27]	II	Platinum ineligible	Atezolizumab	SP142 ≥ 5%	23	2.7	15.9	Single-arm, small sample size, and no randomization
NCT01693562[28]	I/II	Second/cisplatin ineligible	Durvalumab	SP263 ≥ 25%	31.0	Not reached	Not reached	Nonrandomized small sample size
KEYNOTE-045[29]	III	Postplatinum	Pembrolizumab vs chemotherapy	22C CPS ≥ 10	21 vs 11	2.1 vs 3.3	10.3 vs 7.4	PD-L1 cutoff variability; cross-over and randomization issues
JAVELIN Bladder 100[30]	III	Postchemo maintenance	Avelumab + BSC vs BSC	SP263 ≥ 25%	18 vs 12	3.7 vs 2.0	21.4 vs 2.0	Maintenance only in responders/stable disease; selection bias
CheckMate275[31]	II	Postplatinum	Nivolumab	Dako28-8 ≥ 1%	19.9	2.0	8.6	Single-arm
CheckMate032 (NCT01928394)[32]	I/II	Second/postplatinum	Nivolumab	Dako28-8 (exploratory)	24.4	2.8 (1.5–5.9)	9.7 (7.3–16.2)	Nonrandomized, mixed dosing, heterogeneity in patient population
IMvigor130[33]	III	First line	Atezolizumab ± chemo	SP142 ≥ 5%	23	8.2	Not reached	PD-L1 benefit in subset only; inconsistent PFS across subgroups

4. Therapeutic landscape in mUC: trends and directions

The therapeutic landscape of mUC has advanced considerably, as illustrated in Figure 2. Platinum-based chemotherapy remains the cornerstone of first-line management for cisplatin-eligible patients, while carboplatin-based regimens or front-line ICIs are used in those who are cisplatin-ineligible, depending on PD-L1 expression status.[20] The introduction of avelumab as switch-maintenance therapy following response or stable disease after platinum-based chemotherapy has established immunotherapy in the postinduction setting as standard practice. In the second-line setting, ICIs such as pembrolizumab remain a key option for platinum-refractory diseases, whereas targeted therapies such as erdafitinib are recommended for patients harboring susceptible FGFR alterations.[10,17,19] In the third-line and beyond, ADCs such as enfortumab vedotin (EV) and sacituzumab govitecan have further expanded the treatment armamentarium. Overall, these advancements represent a shift toward biomarker-guided decision-making and molecular integration of chemotherapy, immunotherapy, and targeted agents across mUC treatment lines. To provide better clarity, the current therapeutic landscape is discussed in the following sections according to treatment setting and strategy, beginning with historical cytotoxic chemotherapy and progressing through modern immunotherapeutic and biomarker-guided approaches.

4.1Platinum-based chemotherapy

Combination chemotherapy based on platinum agents remains the primary first-line therapy for treatment-naive patients with mUC.[3,13] For cisplatin-eligible patients, the standard therapy is platinum-based chemotherapy, often followed by maintenance therapy with avelumab. For individuals who are unsuitable for cisplatin due to renal impairment or other contraindications, alternative treatments include gemcitabine combined with carboplatin, which may also be followed by avelumab or pembrolizumab maintenance.[35] Another option for this subgroup includes the combination of pembrolizumab with EV.[35] Eligibility for cisplatin-based chemotherapy typically requires a good functional status (ECOG-1 PS ≤1), preserved renal function (creatinine clearance >50-60 mL min^{-1}), and no significant comorbidities.[13,34] Dose-dense M-VAC is an alternative option that has also demonstrated efficacy in mUC treatment.[35] Typically, patients receive 6 cycles of chemotherapy; however, early discontinuation or dose reduction may be necessary due to cumulative toxicity.[36] Despite high initial disease control being achieved in approximately 75% to 80% of patients with first-line platinum-based chemotherapy, durable responses are limited due to the patient frequently developing resistance in many cases.[37] Median OS is typically around 14 to 15 months for those receiving cisplatin-based treatment and approximately 9 to 10 months for those treated with carboplatin, respectively.[37–39]

4.2Immune checkpoint inhibitors (ICIs)

ICIs have brought major advances in the management of mUC, particularly in patients experiencing disease progression following platinum-based chemotherapy.[9] These agents enhance the body's antitumor immune response by blocking key inhibitory pathways, primarily the PD-1/PD-L1 axis and CTLA-4, which cancer cells utilize to evade immune surveillance.[9,11,12] Tumors expressing PD-L1 can inhibit immune activity by engaging PD-1

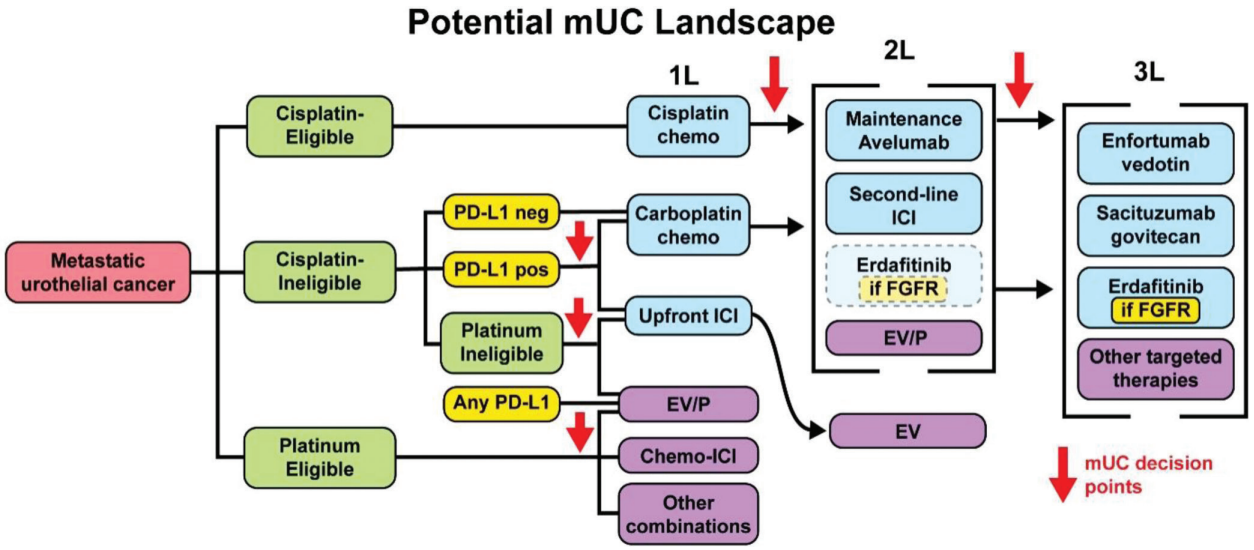

Figure 2. An overview of mUC therapeutic strategies shaped by clinical factors (green), predictive biomarkers (yellow), FDA-approved therapies (blue), and investigational approaches (purple). Chemoimmunotherapy with atezolizumab improved PFS in the IMvigor130 trial (NCT02807636), through OS remains inconclusive. The enfortumab vedotin plus pembrolizumab (EVP) combination is under investigation across multiple settings: as a front-line option vs platinum-based chemotherapy (EV-302, NCT04223856), for cisplatin-ineligible patients (EV-103, NCT03288545), and in the postplatinum settings (EV-103; EV-201, NCT03219333). Additional novel combinations and targeted therapies are actively being explored across various lines of treatment[34]. Copyright 2022, OAE publishing Inc.

receptors on activated CD^+ T cells,[11] a mechanism that can be reversed by monoclonal antibodies targeting this interaction, such as atezolizumab, avelumab, and durvalumab (anti-PD-L1), as well as pembrolizumab and nivolumab (anti-PD-1). Additionally, targeting CTLA-4, another key checkpoint receptor on T cells, with agents like ipilimumab and tremelimumab, promotes T-cell activation and proliferation.[7,12]

Early-phase trials (I–II) of ICIs in platinum-refractory mUC have demonstrated ORR of 15% to 27% with higher rates observed in PD-L1-positive tumors.[5] Notable results included nivolumab (19.6% ORR, 16 months OS), pembrolizumab (28.9% ORR, 11.3 months OS), and atezolizumab (23%% ORR, 16 months OS), while avelumab (18.2% ORR, 13.7 months OS) and durvalumab (17.8% ORR, 18.2 months OS) also showed promise.[3,12] These positive early outcomes led to accelerated regulatory approvals for ICIs in advanced mUC. However, subsequent randomized trials revealed fewer histrionic benefits, resulting in some indications being withdrawn or restricted. For instance, the atezolizumab indication for platinum-refractory mUC was withdrawn after the IMvigor 211 trial failed to demonstrate significant OS improvement.[40]

Currently, pembrolizumab retains full FDA approval for the treatment of mUC in patients who have experienced disease progression following platinum-based chemotherapy or are cisplatin-ineligible.[34,41] Before ICIs, second-line treatment options for mUC were restricted to agents such as pemetrexed, paclitaxel, vinflunine, and docetaxel, all of which showed limited effectiveness with a median OS of ~7 months.[42,43] The KEYNOTE-045 phase-III trial established pembrolizumab as the preferred second-line therapy, demonstrating a significant improvement in OS (median 10.3 months compared with 7.4 months with chemotherapy) and positioning it as a more effective alternative to traditional cytotoxic agents.[44] While efforts to integrate ICIs into front-line treatment settings through monotherapy in biomarker-enriched populations, combination regimens with chemotherapy, or maintenance therapy have been explored, randomized trials have not yet confirmed a meaningful improvement in OS, leaving the role of ICIs in the front-line setting still under investigation.

5. Front-line use of immunotherapy in mUC

The phase-III DANUBE trial (NCT02516241) assessed the efficacy of durvalumab alone and in combination with tremelimumab (a CTLA-4 inhibitor) versus platinum-based chemotherapy in treatment-naive patients with advanced or mUC. Neither approach demonstrated a significant enhancement in OS in contrast to chemotherapy, even among PD-L1-positive patients. Specifically, durvalumab monotherapy achieved a median OS of 14.4 months compared with 12.1 months with chemotherapy (hazard ratio [HR] = 0.89; P = 0.30), while the combination therapy showed a median OS of 15.1 months (HR = 0.85; P = 0.075). A major limitation of front-line immunotherapy has been its lower ORR and shorter PFS relative to chemotherapy. Although ICIs can elicit durable responses in selected patients, their slower onset of action and limited efficacy across broader populations have restricted their use. Thus, single-agent ICIs have not yet replaced chemotherapy as the standard care for first-line mUC. Nevertheless, recent advances in combination strategies are reshaping the mUC therapeutic landscape. Notably, the FDA approval of pembrolizumab in combination with EV marks a significant shift toward effective first-line immunotherapy-based regimens irrespective of cisplatin eligibility. Current clinical trials are actively investigating novel combinations of ICIs with chemotherapeutic agents or other targeted therapies in an effort to enhance response rates and improve long-term survival outcomes for mUC patients.[45,46]

6. Front-line use of immune-chemotherapy combinations in mUC

The integration of ICIs with chemotherapy in the front-line treatment of mUC has yielded inconsistent outcomes. In the phase-III KEYNOTE-361 trial, combining pembrolizumab with

platinum-based chemotherapy did not significantly improve OS compared with chemotherapy alone (median OS: 10.0 versus 14.3 months; HR = 0.86, P = 0.0407, which was not statistically significant at the prespecified alpha level).[40] Similarly, pembrolizumab monotherapy also failed to demonstrate clear superiority. In the IMvigor130 trial, which evaluated atezolizumab combined with platinum-based chemotherapy, there was a modest improvement in PFS (8.2 versus 6.3 months; HR = 0.82; P = 0.007), but no statistically significant OS benefit was observed. Consequently, neither of these ICI-chemotherapy combinations has been widely adopted as a standard first-line treatment for mUC. This lack of strong additive benefit suggests that concurrent administration of chemotherapy and immunotherapy may not generate synergistic effects in mUC, possibly due to unique bladder tumor-specific immunogenic characteristics or differential tumor-immune interactions compared with other cancer types where such combinations have shown greater efficacy.[5,9,12]

7. Maintenance immunotherapy

Maintenance immune therapy has significantly advanced the treatment landscape for mUC-suffering patients. The phase-III JAVELIN bladder 100 trial established avelumab as the standard maintenance therapy for patients achieving disease control after first-line platinum-based chemotherapy. The trial demonstrated a median OS of 21.4 months with avelumab, compared with 14.3 months with best supportive care (BSC) alone (HR = 0.69; P = 0.001). This benefit was consistent across all subgroups, including PD-L1 positive patients, who showed a 1-year survival rate of 79.1% with avelumab versus 60.4% with BSC (HR = 0.56; P < 0.001). Avelumab also significantly improved PFS, with a manageable safety profile, despite a higher incidence of grade ≥3 adverse events.[47] Extended follow-up data further confirmed the durability of these benefits, showing a median OS of 23.80 months compared with 15.0 months with BSC, and a median PFS of 5.5 versus 2.1 months. These results led to avelumab national comprehensive cancer network (NCCN) category 1 recommendation as maintenance therapy for mUC.

Real-world evidence from the READY and AVENANCE studies further validated these findings. Additionally, the CheckMate-901 trial demonstrated the potential of combining nivolumab with cisplatin-based chemotherapy, expanding clinicians' personalized treatment options based on patient-specific factors. As both avelumab and nivolumab continue to shape maintenance strategies, ongoing studies are evaluating combination approaches and subsequent therapies for patients who progress following maintenance.[47] Future research efforts are focused on novel combinations, including ADCs paired with immunotherapy, dual checkpoint inhibition targeting CTLA-4 and PD-L1, and other emerging treatment modalities designed to further improve outcomes in mUC patients.[7,9,11,45]

8. Emerging immune combinations in mUC

Novel immunotherapeutic strategies in mUC increasingly rely on rational combinations to enhance antitumor efficacy beyond monotherapy. A key example is the combination of pembrolizumab with sEphB4-HSA, which targets tumor growth factors EphB4 (on tumor cells) and EphrinB2 (on tumor vasculature), inhibiting tumor angiogenesis and promoting tumor cell apoptosis.[48] Phase-II data showed a 37% ORR overall, with markedly higher benefit in EphrinB2-positive patients (ORR: 52%, complete response (CR): 24%, PFS: 5.7 months, OS: 21.5 months). This type of combination therapy received FDA breakthrough approval in 2021; however, randomized phase-III validation is required. Similarly, the NORSE study (NCT03473743) evaluated erdafitinib plus the anti-PD-1 antibody cetrelimab in cisplatin-ineligible FGFR-mutant patients, reporting an ORR of 68% compared with 33% with erdafitinib alone, emphasizing the value of genomic stratification.[48,49] Conversely, the BISCAY trial (NCT02546661) assessed durvalumab with various targeted inhibitors, such as FGFR, PARP, and mechanistic target of rapamycin (mTOR) inhibitors in biomarker-selected mUC populations, but showed no significant improvement over targeted therapy alone, suggesting that only select combinations yield synergistic immunomodulation. ADCs represent another promising class, whereas EV targets nectin-4 as monotherapy improves OS postchemotherapy and immunotherapy (EV-301). In combination with pembrolizumab (EV-103), EV has shown an ORR of 73.3% in cisplatin-ineligible first-line patients, with phase-III results eagerly awaited (EV-302). Another ADC, sacituzumab govitecan, has demonstrated ORRs of 27% as monotherapy and 35% in combination with pembrolizumab in heavily pretreated mUC patients, with ongoing trials evaluating the potential of immune-ADC combinations in future lines of therapy.[49,50]

9. Biomarkers for precision immunotherapy in mUC

Emerging immune combinations have significantly advanced the therapeutic options for mUC, with biomarker integration playing a crucial role in personalizing treatment. The effective use of biomarkers, such as PD-L1, TMB, and ctDNA, holds great promise in improving patients' selection and treatment outcomes. Nonetheless, their clinical utility is limited by variable predictive value and practical challenges.[17] PD-L1 expression, while extensively studied, suffers from methodological inconsistencies, including differences in antibody clones, scoring systems, and tumor versus immune cell expression, which affect its reliability as an individual biomarker.[22] TMB, a surrogate for neoantigen load, has shown promise in predicting responses to immunotherapy but is influenced by intertumoral heterogeneity and lacks standardized cutoff values, limiting its widespread adoption. ctDNA has emerged as a dynamic tool for detecting minimal residual disease (MRD) and guiding adjuvant therapy decisions,[50] with the IMvigor010 trial demonstrating that ctDNA-positive patients have a higher risk of relapse and benefit from adjuvant atezolizumab (HR = 0.58; P = 0.0024).[40] Despite its potential, ctDNA's clinical implementation is constrained by logistical barriers, including assay availability, turnaround time, and cost. Additionally, emerging biomarkers, such as T-effector gene signatures, APOBEC mutagenesis, TGF-β signaling, and natural killer (NK) and macrophage signatures, are being investigated for their predictive value but remain in the exploratory phase, requiring further validation.[34] The role of tertiary lymphoid structure (TLS), associated with robust immune responses, is also under investigation but requires more evidence before clinical integration. The development of multimodal biomarker strategies, combining mutational profiles with immune-related signatures, aims to enhance patient selection and treatment prediction. As illustrated in Figure 3, biomarker research in mUC is evolving from traditional markers like PD-L1 toward more comprehensive, combinational-induced approaches, particularly after the introduction of EV and EVP.[51]

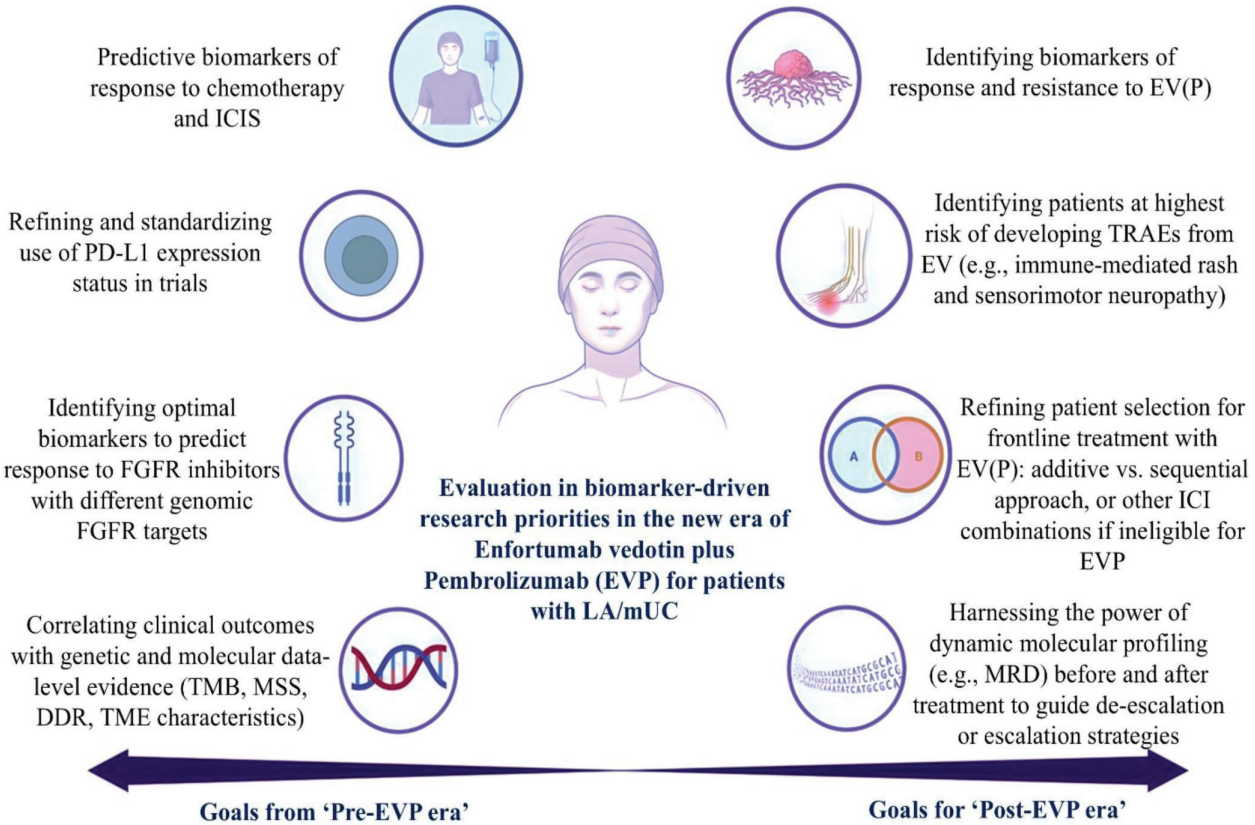

Figure 3. Evolving directions in biomarker research aligned with the establishment of EVP as the new standard of care in mUC. Key focus areas include DNA damage response and repair (DDR), FGFR alterations, molecular residual disease (MRD), microsatellite status (MSS), TMB, TME, and PD-L1 expression[51]. Copyright 2024, MDPI.

However, real-world integration of these biomarkers remains challenging due to inconsistent predictive value, a lack of harmonization, and the absence of robust composite models. As summarized in Table 3, overcoming these limitations through multiplatform biomarker strategies is critical for advancing precision immunotherapy in mUC, guiding therapeutic combinations, and optimizing patient selection for personalized therapy.[10,16,20,28,52]

9.1Advanced drug-delivery systems to enhance immunotherapy in mUC

While ICI-based therapies have demonstrated significant promise in the treatment of mUC, their clinical efficacy is often hampered by poor tumor penetration, systemic toxicity, and suboptimal immune activation in the TME. Advanced drug-delivery systems (DDS) offer potential solutions to these challenges by improving the specificity and effectiveness of immunotherapy in mUC.[53] Notably, nanocarriers, such as PD-1/PD-L1 antibody-loaded nanoparticles, allow for targeted delivery of ICIs directly to the tumor site.[22] This strategy enhances tumor penetration, sustains high local drug concentrations, and minimizes systematic toxicity. By utilizing the enhanced permeability and retention effect, these nanoparticles can preferentially accumulate in tumor tissues, improving the efficacy of immunotherapy while reducing side effects commonly seen under general treatments. Furthermore, biomaterial scaffolds have shown promise for localized immune activation, with potential applications in mUC. These scaffolds can be implanted directly into or near the tumor, where they release ICIs, cytokines or immune-stimulating agents in a controlled manner.[54] This localized delivery enhances the recruitment of TILs and activates immune responses in the TME. Such biodegradable scaffolds have the advantage of promoting sustained immune surveillance while reducing the need for repeated administration. Although challenges remain in terms of biocompatibility, long-term toxicity, and scalable manufacturing, ongoing research is continuously exploring the clinical integration of these DDS with conventional therapies to address these hurdles (Table 4). These innovations can substantially improve response rates, minimize adverse effects, and contribute to more durable outcomes for mUC patients.

10. Toxicity comparisons and management of ICIs in comorbid populations in mUC

10.1Toxicity comparisons across ICI regimens

ICIs have shown significant promise in the treatment of mUC; however, their clinical application is often hindered by immune-related adverse events (irAEs). These adverse events, which may affect multiple organ systems, can range from mild to severe, and their incidence varies depending on the specific therapeutic regimen. Common irAEs associated with ICIs include dermatitis, colitis, hepatitis, pneumonitis, and endocrinopathies.[60] In combination regimens, particularly those involving ICI (e.g., pembrolizumab or atezolizumab) in conjugation with chemotherapy, the occurrence of irAEs tends to be higher, with some trials demonstrating increased toxicity profiles due to the

Table 3

Summary of biomarkers in immunotherapy for mUC.

Biomarker	Description	Predictive value	Clinical integration	Limitations
PD-L1 expression	Expression of PD-L1 on tumor or immune cells, used to predict response to ICIs (e.g., pembrolizumab, atezolizumab)	Predicts response in some studies but lacks consistency across trials	Widely used in clinical trials, but inconsistent across patient populations	Methodological variability (antibody clones, scoring systems), tumor vs immune cell expression discrepancies
TMB	Total number of mutations in tumor DNA, indicative of neoantigen load	Higher TMB correlates with better response to ICIs in some cancers	Evolving as a predictive tool requires further standardization	Intertumoral heterogeneity, lack of standardized cutoff values, and context-dependent
ctDNA	Fragments of tumor DNA found in blood, used to detect MRD and guide treatment decisions	High ctDNA levels associated with relapse risk may predict benefit from adjuvant therapy	Promising for MRD detection and relapse prediction, but clinical implementation remains limited	Assay availability, turnaround time, and cost limitations, still in the validation phase
T-effector gene signature	Expression profiles indicative of immune response, including T-cell activation and cytokine production	Correlates with response to ICIs in some studies	Currently exploratory, could become part of multimodal strategies in the future	Need further validation in mUC and may not apply uniformly to all patients
APOBEC mutagenesis	Gene mutations caused by APOBEC family enzymes, associated with tumor evolution	Linked better response to immune therapies in some cancers	Requires further research and prospective validation	Still under investigation with limited data in mUC
TGF-β pathway activity	Inhibition of immune responses via TGF-β, a key immune-suppressive factor	Higher TGF-β signaling may correlate with poor response to immunotherapy	Ongoing studies; potential to combine with ICIs or targeted therapies in the future	Biomarker and pathways exploration are still in early stages
NK cells and macrophages	Immune cells involved in tumor surveillance and response to ICIs	Correlated with better immune response in some cancers	It could inform patient selection in combination therapies; it needs further exploration	Still under investigation and inconsistent findings in mUC
TLS	Lymphoid-like structures in tumors associated with immune activation	Associated with better prognosis and response to immunotherapy	Promising as a biomarker for immune activity, further studies are needed	Limited data on how TLS specifically impacts ICIs in mUC

additive effects of chemotherapy. For instance, the combination of pembrolizumab with cisplatin or gemcitabine has been associated with enhanced efficacy but also increased risks of severe toxicity, including myelosuppression and gastrointestinal distress.[60,61] Conversely, regimens incorporating ADCs, such as EV and EVP, often show a more favorable toxicity profile. Despite this, concerns persist in terms of dose-limiting toxicities, including peripheral neuropathy and gastrointestinal issues, specifically associated with the cytotoxic payload of ADCs. Importantly, while immune-chemotherapy combinations demonstrate improved OS and PFS outcomes, they also necessitate careful patient selection and monitoring due to their heightened risk of severe irAEs.[60] ADC-based regimens, while showing promising efficacy, are exhibiting distinct toxicities related to payload, which can lead to dose-limiting adverse effects that require close clinical supervision.

10.2Management of ICIs in comorbid populations

The management of ICIs in mUC patients with comorbidities presents additional challenges, as these patients often exhibit altered immune responses and may experience exacerbated or prolonged toxicities. Common comorbid conditions in mUC patients include cardiovascular disease, diabetes, renal impairment, and prior treatments, all of which can influence the tolerability and safety of ICIs.[62] For example, patients with pre-existing renal dysfunction may be at a high risk for nephrotoxicities when treated with cisplatin-based regimens or may have heightened susceptibility to ICIs, particularly if they are receiving concurrent immunosuppressive therapy. In these cases, the renal clearance of ICIs may be impaired, necessitating dose adjustments or alternative treatments.[61] Additionally, patients with diabetes or cardiovascular disease may be more prone to immune-related endocrinopathies, such as thyroiditis or adrenalitis, which require careful management to prevent life-threatening complications. Patients with autoimmune conditions represent another high-risk group for the development of severe irAEs.[60] These individuals may experience exacerbations of their autoimmune disease due to the activation of immune responses by ICIs. Such conditions warrant a more cautious approach, with close monitoring for early signs of autoimmunity or organ-specific toxicity. In these settings, the use of corticosteroids or other immunosuppressive therapies may be necessary to manage severe irAEs, but their use should be balanced against the potential risk of reducing the efficacy of ICIs.[61] Furthermore, the combination of ICIs with other organized therapies, such as targeted therapies or chemotherapy, in patients with comorbid conditions requires careful consideration due to potential drug–drug interactions. These interactions may not only amplify the toxicity of ICIs but also complicate the management of pre-existing health issues in these populations.

10.3Presence of multiple comorbidities, poor PS, and advanced age

Patients with multiple comorbidities, poor PS, and advanced age are frequently underrepresented in ICI clinical trials, raising concerns among oncologists regarding the feasibility of ICI treatment in these populations. These patients often have limited physiologic reserves, which may hinder their ability to tolerate treatment-related toxicities or recover from adverse events.[63] Consequently, clinicians are often cautious about offering ICIs to these individuals, as they may be less likely to derive a survival benefit from immunotherapy due to the potential exacerbation of existing comorbid conditions.

A retrospective analysis conducted by Clark-Garvey et al.[64] demonstrated that progression of disease was the most common cause for discontinuation of ICIs in patients with varying ECOG PS. Of particular interest, the study found that a higher proportion of patients with PS of 1 (17%) or PS of 2/3 (5.6%),

Table 4

Advanced DDS for immunotherapy in mUC.

DDS type	Description	Benefits	Challenges
Nanoparticles (PLGA)[55]	Encapsulate ISIs like PD-1/PD-L1 antibodies in polymeric nanoparticles for targeted delivery	Increased tumor penetration, sustained release, and reduced systemic toxicity	Limited scalability and potential immune rejection
Mesoporous silica nanoparticles[56]	Nanosized porous particles for drug-controlled drug release	High loading capacity, prolonged drug-release, and targeted delivery	Risk of inflammation and long-term biocompatibility
Liposomes[57]	Lipid-based carriers that deliver ICIs directly to the tumor site	Improved drug stability, enhanced bioavailability, and controlled release	Biodegradability concerns and manufacturing challenges
Hydrogels[58]	Injectable gels that release immune stimulants and ICIs locally	Sustained release, easy to implant, and can be tailored to the tumor site	Limited control over release kinetics and potential inflammatory response
Biomaterial scaffolds (mesoporous silica)[59]	Implantable scaffolds that release ICIs or cytokines locally	Localized immune activation, reduced systemic exposure, and continuous drug release	Biocompatibility and long-term implantation effects

highlighting the heterogeneity of treatment tolerance based on PS. Additionally, the analysis of the Charleston Comorbidity Index (CCI), which quantifies comorbidities and their relationship to 1-year mortality, indicated that patients who discontinued therapy due to disease progression, irAEs, or exacerbation of comorbidities had similar CCI scores, further emphasizing the complexity of treatment decisions in patients with multiple comorbidities.

Furthermore, the safety profile of ICIs in elderly patients remains a critical consideration. A study performed by Singh et al.[65] revealed that adverse events requiring discontinuation occurred in 17.1% of patients aged 65 or older compared with 14.4% in those under 65 years old. Although no significant differences in toxicity were observed between these age groups, elderly patients showed a higher incidence of diarrhea and colitis (4.1%) compared with their younger counterparts (2.4%), which may have implications for managing irAEs in this population. Similarly, a meta-analysis by Elias et al.[66] concluded that ICIs such as nivolumab, pembrolizumab, and atezolizumab provide comparable efficacy in both elderly and younger patients, although age-related differences in toxicities and the physiological reserve of elderly patients must be carefully considered.

In patients with poor PS (ECOG 2 or 3), retrospective studies have shown that ICIs can still offer clinical benefit. A study presented by Pietrantonio et al.[67] indicated that a subset of patients with poor PS experienced meaningful responses to ICIs, with 33% showing a response and a median duration of 16.9 months. These findings suggest that poor PS may be reversible with effective therapy, and that some patients, particularly those with biomarkers predictive of ICI response (e.g., PD-L1 expression, microsatellite instability-high), may benefit from immunotherapy despite their frailty.

10.4Strategies for managing toxicity in comorbid populations

To optimize clinical outcomes for ICI therapy in patients with comorbidities, a personalized approach is crucial. Integrating a multidisciplinary team of oncologists, pharmacologists, and specialists is key to balancing immunotherapy efficacy and managing comorbidity-related risks. Close monitoring and real-time management of irAEs, with particular attention to organ-specific toxicities, are essential for maintaining the safety of ICIs in these populations. Tailored strategies based on individual patient profiles, such as dose modifications, biomarker-driven selection of candidates, and early intervention for irAEs, may enhance both safety and efficacy of ICI therapy in mUC patients with comorbidities, advanced age, or poor PS.

11. Future perspectives

Immunotherapy has profoundly transformed the therapeutic landscape for mUC patients, offering the potential for durable responses and prolonged remission. However, significant challenges persist in optimizing patient selection, refining treatment timing, and enhancing overall efficacy. Current immune strategies are often implemented at later disease stages, and the absence of robust predictive biomarkers continues to impede precision medicine. Therefore, future directions must prioritize 3 key areas, including enhancing therapeutic combinations, advancing biomarker development, and optimizing treatment settings.

The first priority is the development of more effective therapies and rational combinations. ADCs, ICIs, and targeted agents represent the forefront of this evolution. EV, an ADC targeting Nectin-4, has demonstrated high ORR, particularly when combined with pembrolizumab, with phase-II trials showing an ORR of >70%. The ongoing EV-302 trial is anticipated to confirm these results and potentially establish a new standard of care in the front-line setting. Similarly, the combination of pembrolizumab with sEphB4-HSA in EphrinB2-positive tumors showed an ORR of 52% and a CR of 24%, with extended OS. In FGFR-mutant populations, the NORSE trial found that erdafitinib plus cetrelimab achieved a 68% ORR in cisplatin-ineligible patients, suggesting this targeted-immunotherapy combination may be synergistic and worthy of phase-III validation. Moreover, dual checkpoint blockade remains under investigation, with trials like CheckMate-901 and NILE exploring CTLA-4 and PD-1/PD-L1 inhibition with or without chemotherapy. Emerging ADCs, such as sacituzumab govitecan and RC48, are also advancing both as monotherapies and in combination with ICIs, showing promising preliminary activity.[68] These advancements in therapeutic combinations emphasize the potential for increasing the depth and duration of responses in mUC.

The second crucial pillar involves advancing biomarker science to enable better patient stratification and personalized treatment. While PD-L1 expression has been extensively studied as a predictive biomarker, its clinical utility in mUC remains inconsistent, preliminary due to methodological variability in testing, such as differences in antibody clones and scoring systems. Consequently, PD-L1's impartial role in patient selection for immunotherapy is increasingly questionable, and multidimensional biomarker strategies are gaining importance. The utility of TMB as a marker for neoantigen load has shown promise in predicting responses to immunotherapy, but its predictive value remains influenced by intertumoral heterogeneity and the lack

of standardized cutoff values, limiting its consistency across studies. ctDNA, a dynamic marker for MRD, has demonstrated potential in guiding adjuvant immunotherapy decisions, particularly in patients with high ctDNA levels, as highlighted by the IMvigor010 trials. However, despite its promise, ctDNA's clinical implementation remains hampered by logistical barriers, such as assay availability, cost, and turnaround time. Emerging biomarkers, including T-effector gene signatures, APOBEC mutagenesis patterns, and TGF-β pathway activity, provide insights into the immune response and TME but require further validation.[16,17] Additionally, biomarkers related to NK cells, macrophage signatures, and TLS are being explored; however, their clinical application remains limited without more robust evidence. Based on these challenges, future biomarker research will likely focus on multiplatform strategies, integrating tumor genomics, immune signatures, and TME features to create more comprehensive patient profiles. Techniques such as single-cell RNA sequencing, spatial transcriptomics, and epigenetic profiling, including circulating methylation signatures, are expected to provide deeper insights into tumor-immune dynamics, offering a more personalized approach to immunotherapy.[34]

The third strategic imperative is the optimization of treatment timing and sequencing based on disease progression and therapeutic response. Administering immunotherapy earlier, particularly in the neoadjuvant or perioperative setting, may maximize benefits by targeting tumor evolution at a less resistant stage. Combining therapies preoperatively, potentially guided by molecular monitoring like ctDNA, could enhance curative potential. Additionally, ICIs are expanding beyond the metastatic setting. For example, ICIs have demonstrated promising results in both non–muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC).[69] Pembrolizumab is already approved for BCG-unresponsive NMIBC in cystectomy-ineligible patients, and adjuvant nivolumab postcystectomy in MIBC has shown significant promise. Optimizing the sequencing of ICIs with other modalities could yield greater clinical benefits and potentially redefine treatment paradigms for earlier-stage disease.

In summary, the future of precision immunotherapy in mUC will be shaped by the synergistic integration of more effective drugs, advanced DDS, refined biomarker-guided patient stratification, biological understanding, and optimization of treatment timing. The ultimate success will depend on the development of multimodal therapies, informed by comprehensive biomarker profiles that guide personalized therapeutic decisions. Advanced DDS, such as nanocarriers for targeted ICIs delivery and biomaterial scaffolds for localized immune activation, hold significant promise in addressing the limitations of current treatments by enhancing the efficacy, specificity, and durability of immune responses. DDS technologies can ensure that immunotherapy agents are delivered directly to tumor sites, minimizing systematic toxicity and maximizing therapeutic effects. As we move into this next era, important advances in both therapeutic agents, drug-delivery technologies, and biomarker science will be critical to improving clinical results. By optimizing DDS alongside precision biomarkers-guided patient selection, treatments can be better tailored to the unique tumor and immune profiles of individual patients, thus ultimately enhancing both the effectiveness and safety of immunotherapy for mUC patients.

12. Conclusions

Platinum-based chemotherapy remains the standard front-line option in mUC, offering superior initial tumor control, but its effectiveness is often limited by its chemoresistance. The integration of ICIs, particularly avelumab as maintenance therapy following chemotherapy, provides a durable survival benefit by combining early cytoreduction with sustained immune activity. While first-line ICI monotherapy and chemotherapy-ICI combinations have demonstrated consistent improvement in OS, combinations like EVP are redefining treatment algorithms, resulting in significantly higher response rates. The future of mUC therapy demands precision medicine, guided by biomarkers like ctDNA, TMB, PD-L1, FGFR alterations, and T-effector signatures, as well as innovations in advanced DDS to enhance therapeutic targeting and minimize toxicity. The current ongoing trials aim to optimize therapeutic combinations and sequencing, advancing toward a more personalized, biomarker-driven standard of care that integrates multimodal therapies for improved outcomes in mUC patients.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

Author Contributions

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