INTRODUCTION

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is the most prevalent type of bladder cancer, accounting for over 90% of cases globally and ranking 10th in terms of cancer incidence [1]. UC typically affects the mucosal epithelial lining of the urinary tract. When it manifests as muscle-invasive bladder cancer (MIBC), it is often discovered in an advanced, metastatic state. Although relatively rare, UC can also involve the upper ureter and renal pelvicalyceal system, a condition known as upper tract urothelial carcinoma (UTUC), which is associated with a poor prognosis [1]. For several decades, cisplatin-based chemotherapy has been the cornerstone of treatment for advanced UC. However, the advent of innovative immunotherapies, including immune checkpoint inhibitors (ICIs), has shifted the focus of UC treatment towards the use of immunotherapy at all stages of the disease [2].

ICIs function by targeting T-cell mediated antitumor responses through associated immune proteins, with the most extensively studied being programmed cell death protein 1 (PD-1) and its ligand (PD-L1). Initially, ICIs were investigated as subsequent treatment options for patients who showed progression after chemotherapy. However, they have demonstrated a durable response not only in adjuvant settings but also in neoadjuvant and maintenance contexts. The introduction of newer agents like nivolumab and atezolizumab has broadened the use of ICIs, resulting in encouraging results in clinical trials for UC. This review offers a concise summary of key studies across various clinical stages and highlights ongoing clinical trials that could potentially impact UC treatment.

Key Words: Urinary bladder neoplasms, Immune checkpoint inhibitors, Transitional cell carcinoma

Traditional cisplatin-based chemotherapy has long been the mainstay treatment for advanced urothelial carcinoma (UC), but the emergence of immune checkpoint inhibitors (ICIs) and immunotherapy has revolutionized the field. ICIs, which target crucial immune proteins such as programmed cell death protein 1 (PD-1) and its ligand (PD-L1), enhance T-cell-mediated antitumor responses and have shown sustained responses not only in adjuvant settings but also in neoadjuvant and maintenance contexts. The introduction of newer agents like nivolumab and atezolizumab has broadened the use of ICIs, resulting in encouraging results in clinical trials for UC. This review offers a concise summary of key studies across various clinical stages and highlights ongoing clinical trials that could potentially impact UC treatment.

Key Words: Urinary bladder neoplasms, Immune checkpoint inhibitors, Transitional cell carcinoma
and atezolizumab, following pembrolizumab, has further broadened the indications. This review aims to provide a summary of the results from practice-changing studies across different clinical stages, as well as upcoming clinical trials.

**IMMUNE CHECKPOINT INHIBITORS IN THE ADJUVANT SETTING**

Cisplatin-based chemotherapy continues to be the first-line treatment for locally advanced or metastatic UC. A phase III trial, JAVELIN Bladder 100 (NCT02603432), demonstrated that additional maintenance therapy with avelumab can enhance treatment durability in patients who have undergone platinum-based chemotherapy as their initial treatment [3] (Table 1). Among 700 patients, those who were randomized to receive avelumab maintenance showed an improved overall survival (OS) rate of 71.3% at 1 year, compared to 58.4%, and a superior median OS of 21.4 months versus 14.3 months. The progression-free survival (PFS) was 3.7 months with avelumab, compared to 2.0 months in the control group. The treatment was generally well tolerated, with only 7% of patients experiencing grade 3 complications.

In cohorts ineligible for platinum treatment, pembrolizumab is a viable first consideration. Initially, it was evaluated as a second-line option for those who showed progression after initial chemotherapy. The KEYNOTE-045 trial demonstrated that pembrolizumab improved the median OS to 10.3 months, compared to 7.4 months, with fewer grade ≥3 adverse events [4]. At 2 years, pembrolizumab consistently outperformed other chemotherapies, including paclitaxel, docetaxel, and vinflunine, in terms of median 1- and 2-year OS (44.2%) [5]. The KEYNOTE-052 trial assessed the role of pembrolizumab as a first-line treatment for advanced UC.

### Table 1. Summary of key practice-changing clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Total patients</th>
<th>ICI</th>
<th>Treatment setting</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMvigor 130 &amp; 211 (NCT02807636 &amp; NCT02108652) [8, 13, 14]</td>
<td>III</td>
<td>1213 &amp; 931</td>
<td>Atezolizumab</td>
<td>First-line combination with chemotherapy &amp; second line</td>
<td>OS 16.0 months with combination in first-line vs. 13.4 months with chemotherapy only (HR, 0.83; 95% CI, 0.69–1.00; p=0.027); Did not meet the endpoint for first-line therapy. Was not favorable compared to chemotherapy as second-line therapy, but showed better durability</td>
</tr>
<tr>
<td>CHECKMATE 274 (NCT02632409) [10]</td>
<td>III</td>
<td>709</td>
<td>Nivolumab</td>
<td>Adjuvant</td>
<td>DFS with nivolumab in an intent-to-treat analysis 20.8% (95% CI, 16.5–27.6) vs. 10.8% (95% CI, 8.3–13.9) in placebo 6-Month DFS 74.9% with nivolumab in an intent-to-treat analysis vs. 60.3% in placebo (HR, 0.70; 98.22% CI, 0.55–0.90; p&lt;0.001) 6-Month DFS 74.5% in PD-L1 ≥1% vs. 55.7% in placebo (HR, 0.55; 98.22% CI, 0.35–0.85; p&lt;0.001)</td>
</tr>
<tr>
<td>KEYNOTE-045 (NCT02256436) [4, 5]</td>
<td>III</td>
<td>542</td>
<td>Pembrolizumab</td>
<td>Adjuvant, second-line after chemotherapy</td>
<td>OS 10.3 months with pembrolizumab vs. 7.4 months with chemotherapy (HR, 0.73; 95% CI, 0.59–0.91; p=0.002); OS in PD-L1≥10% 80.0 months with pembrolizumab vs. 5.2 months with chemotherapy.</td>
</tr>
<tr>
<td>KEYNOTE-052 (NCT02335424) [28, 69]</td>
<td>II</td>
<td>374</td>
<td>Pembrolizumab</td>
<td>First-line, Cisplatin-ineligible</td>
<td>ORR 24% (95% CI, 20–29); Better ORR in PD-L1≥10% group (38%; 95% CI, 29–48) 2-Year ORR 28.6% (95% CI, 24.1–33.5) OS 11.3 months, with 46.9% 1-year OS &amp; 31.2% 2-year OS</td>
</tr>
<tr>
<td>JAVELIN Bladder 100 (NCT02603432) [3]</td>
<td>III</td>
<td>700</td>
<td>Avelumab</td>
<td>Maintenance after chemotherapy</td>
<td>1-Year OS 91.3% with avelumab vs. 58.4% in control (median OS 21.4 vs. 14.3 months; HR, 0.69; 95% CI, 0.56–0.86; p=0.001); 1-Year OS in PD-L1 positive 79.1% with avelumab vs. 60.4% in control (HR, 0.56; 95% CI, 0.40–0.78; p&lt;0.001).</td>
</tr>
<tr>
<td>PURE-01 (NCT02736268) [17, 18, 70]</td>
<td>II</td>
<td>143</td>
<td>Pembrolizumab</td>
<td>Neoadjuvant</td>
<td>3-Year PFS 84.4% and OS 83.8 in an intent-to-treat analysis. High PD-L1 expression strongly correlated with sustained response.</td>
</tr>
</tbody>
</table>

ICI, immune checkpoint inhibitor; OS, overall survival; HR, hazard ratio; CI, confidence interval; DFS, disease-free survival; PD-L1, as programmed cell death protein 1; ORR, overall response rate.
in patients ineligible for cisplatin [6]. The initial results from the phase II study were promising, with a 24% objective response rate (ORR) at a median of 5 months. However, the KEYNOTE-361 phase III trial yielded negative results, leading to the restriction of pembrolizumab use to only cisplatin-ineligible patients. This decision was made because the addition of pembrolizumab did not improve PFS or OS compared to chemotherapy alone, at a median follow-up of 31.7 months [7].

Atezolizumab encounters similar limitations due to the reduced survival rate with ICI monotherapy compared to chemotherapy, as observed in the IMvigor130 trial. This is because the combination of atezolizumab and chemotherapy did not demonstrate a statistically significant OS benefit [8]. The first completed phase III trial, IMvigor010 (NCT02450331), also failed to show an improvement in disease-free survival (DFS) with adjuvant atezolizumab compared to observation in a study involving 809 patients [9]. Although generally tolerable, the DFS was comparable between the experimental and control groups at a median follow-up of 21.9 months (19.4 months vs. 16.6 months, respectively, p=0.24). In contrast, the CHECKMATE-274 trial (NCT02632409) revealed that in high-risk MIBC, adjuvant nivolumab following RC resulted in a longer DFS of 20.8 months compared to 10.8 months with a placebo in the intention-to-treat population. Furthermore, 77.0% of patients were alive and free from recurrence outside the urothelial tract with nivolumab, compared to 62.7% with a placebo [10]. A PD-L1 expression level of 1% or higher was positively associated with better survival. The results from the prematurely terminated AMBASSADOR trial (NCT03244384), which stopped after 95% accrual due to the U.S. Food and Drug Administration (FDA) approval of nivolumab, are eagerly anticipated.

Durvalumab initially received FDA approval in 2017, based on the promising results of an early phase I/II multicenter trial involving 191 participants [11]. The ORR was 17.8%, with 7 complete remissions and a better response in the PD-L1 high group (27.6% vs. 5.1% in PD-L1 negative). The median PFS and OS were 1.5 and 18.2 months, respectively. However, the subsequent DANUBE trial, which compared durvalumab alone, durvalumab plus tremelimumab, and chemotherapy in a large cohort of 1,126 patients, yielded negative results. It failed to meet either of its primary endpoints (OS in the high PD-L1 population and the intent-to-treat population). There was no clear survival benefit of the durvalumab and tremelimumab combination over standard chemotherapy, leading to the voluntary withdrawal of durvalumab’s indication for advanced UC [12]. Atezolizumab experienced a similar outcome, with the IMvigor211 phase III trial in 931 patients treated with atezolizumab failing to meet the primary endpoint of OS [13]. No significant difference in OS was observed (11.1 months vs. 10.6 months with chemotherapy, p=0.41), although atezolizumab did demonstrate better durability (15.0 months vs. 7.3 months). Despite its withdrawal in 2021, atezolizumab remains included in the NCCN guidelines as an option for first-line therapy in cisplatin-ineligible patients. This is likely due to long-term evidence from the trial showing a better 2-year OS with atezolizumab (23%) compared to chemotherapy (13%) at a median follow-up of 33 months [14].

Research is scarcer on UTUC. The only phase III randomized trial using platinum-based combination chemotherapy, known as the POUT trial, did provide evidence of improved DFS with adjuvant therapy administered within 90 days of surgery (HR, 0.45; 95% CI, 0.30–0.68; p=0.0001) [15]. However, trials involving ICIs have yielded inconsistent results. The IMvigor010 [9] and Checkmate 274 [10] trials offered evidence through a subgroup analysis in a predominantly MIBC cohort. The use of atezolizumab in 54 UTUC patients (6.7%) showed no significant difference in median DFS compared to a placebo (19.4 months vs. 16.6 months, p=0.24). The CHECKMATE-274 trial, which used adjuvant nivolumab, included a larger sample of 149 UTUC patients (21%) out of a study population of 709. When stratified by tumor location, bladder UC patients clearly benefited in terms of disease recurrence or death with adjuvant nivolumab (HR, 0.62; 95% CI, 0.49–0.78). However, UTUC patients with tumors in the renal pelvis (HR, 1.23; 95% CI, 0.67–2.23) and ureter (HR, 1.56; 95% CI, 0.70–3.48) showed no difference compared to a placebo. A recent meta-analysis by Laukhitina et al. [16] supports these findings, showing that chemotherapy is associated with less change in disease progression (HR 0.36, 95% CI 0.13–0.92), while atezolizumab and nivolumab...
did not improve PFS (HR, 1.39; 95% CI, 0.28–7.25 and HR, 1.21; 95% CI, 0.29, respectively). Thus, at least in patients with UTUC, there is limited evidence to advocate the use of immunotherapy over chemotherapy in adjuvant settings.

**IMMUNE CHECKPOINT INHIBITORS IN THE NEOADJUVANT SETTING**

The role of ICIs has been further explored in the neoadjuvant treatment of UC, with results currently available from 2 phase II trials. The PURE-01 trial examined patients with advanced or metastatic UC who received 3 cycles of neoadjuvant pembrolizumab before undergoing cystectomy [17]. Out of 50 patients, 21 (42%) achieved the primary endpoint of pT0 response, with 27 (54%) experiencing downstaging. The study found a particularly significant benefit in patients with high PD-L1 expression and tumor mutational burden (TMB), indicating a promising role for these subgroups. An updated report in 2020 demonstrated benefits in patients with variant histology (VH), primarily squamous cell carcinoma or lymphoepithelioma-like variants. In this report, 16% and 53% of predominant and nonpredominant VH subgroups achieved pT0, respectively, compared to 39% in pure UC [18]. The ABACUS trial (NCT02662309) evaluated 95 patients who received 2 cycles of neoadjuvant atezolizumab [19, 20]. Upon pathological examination, a complete response was achieved in 31% of patients, with pre-existing T-cell immunity identified as a strong predictor of treatment success, particularly in cases with elevated intraepithelial CD8+ cell expression [19]. After a median follow-up of 25 months, the 2-year DFS was 68% and OS was 77%. Baseline PD-L1 and TMB did not correlate with survival outcomes [20].

Two randomized phase III trials, KEYNOTE-866 (NCT3924856) [21] and KEYNOTE-905/EV-303 [22] (NCT03924895), are currently in progress. These trials aim to assess the effects of perioperative pembrolizumab compared to a placebo, as well as the effects of pembrolizumab monotherapy versus a combination of pembrolizumab and enfortumab vedotin. KEYNOTE-866 is designed for patients who are eligible for cisplatin treatment, while KEYNOTE-905/EV-303 is intended for those who are not eligible for cisplatin treatment [22].

Neoadjuvant ICI therapy may provide greater benefits to patients with UTUC, particularly as subsequent nephroureterectomy in those eligible for surgery inevitably carries the risk of impairing renal function. This makes postoperative cisplatin-based chemotherapy more challenging [23]. However, similar to adjuvant therapy, the studies are confined to subcohort analyses and have not yielded encouraging results. PURE-02, a phase II feasibility trial, enrolled a small group of 10 UTUC patients to undergo 3 cycles of neoadjuvant pembrolizumab before surgery [24]. Only 1 patient exhibited a complete response, while the others showed no pathologic benefit.

**IMMUNE CHECKPOINT INHIBITORS FOR NON–MUSCLE-INVASIVE BLADDER CANCER**

Non-muscle-invasive bladder cancer (NMIBC) represents a distinct patient category. Despite a relatively high cure rate, a significant proportion of UC that initially presents as NMIBC progresses to MIBC. This is particularly true when poor prognostic features such as carcinoma in situ (CIS), VH, or high grade are also present [25]. Approximately 50% of NMIBC patients treated with intravesical bacillus Calmette-Guérin (BCG) either do not respond (BCG-refractory) or experience a recurrence after initial success (BCG-relapsing) [26]. Treatment for these groups is further complicated by a global shortage of BCG and suboptimal responses to intravesical mitomycin C or gemcitabine. Consequently, the use of ICIs has been recently explored, yielding promising results [27].

The KEYNOTE-057 trial assessed the use of pembrolizumab monotherapy in 101 patients suffering from BCG-unresponsive bladder cancer [28]. After treatment, a complete response was observed in 41% of patients at the 3-month mark. At a median follow-up period of 36.4 months, 28% of patients remained disease-free. Treatment-related adverse events were reported by 13% of patients, with serious treatment-related adverse events occurring in 8% of patients. These findings led to the FDA approval of pembrolizumab in 2020 for high-risk, BCG-unresponsive NMIBC patients who are unable to undergo cystectomy. In a similar vein, the SWOG S1605 trial investigated the use
of atezolizumab, administered every 3 weeks for a year, in 135 patients [29]. After 3 months, 41.1% of patients had a complete response, with 29% remaining disease-free at the 18-month mark. The treatment was generally well tolerated, with serious adverse events reported in 17% of patients, including 2 mortality cases, one of which was treatment-related.

Several key phase III clinical trials are currently in progress. For instance, CHECKMATE 7G8 (NCT04149574) is designed to evaluate the role of nivolumab in populations that have relapsed after BCG treatment [30]. CREST (NCT04165317), ALBAN (NCT03799835), KEYNOTE-676 (NCT03711032), and POTOMAC (NCT03528694) [31] are aimed at BCG-naïve patients. These trials are testing the combination of ICI with BCG as a first-line therapy in NMIBC. The trials are using sasanlimab, atezolizumab, pembrolizumab, and durvalumab, respectively.

**ROLE OF COMBINATION THERAPY**

Based on the success of individual agents, numerous trials have explored the role of dual ICI combinations. The TITAN-TCC trial implemented a response-oriented strategy for patients with advanced UC who had previously undergone platinum-based treatment [32]. All 83 participants initially received induction with nivolumab monotherapy. This was followed by continued nivolumab treatment for those who showed either partial or complete responses. The remaining participants received an added combination of ipilimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor, in conjunction with nivolumab. The initial ORR of 20.5% with nivolumab induction increased to 32.5% with the addition of ipilimumab. Notably, the response rate was significantly higher in the PD-L1 positive subgroup (46% vs. 24% in the PD-L1 negative group). The median PFS and OS were 1.9 months and 7.6 months, respectively.

In the CheckMate-032 trial, a similar group of 274 patients with advanced UC who had previously undergone platinum chemotherapy was randomly assigned to either nivolumab as monotherapy or one of 2 different regimens of nivolumab combined with ipilimumab [33, 34]. The best objective response was observed with a higher dose of ipilimumab, at 42%, compared to a high dose of nivolumab (26%) or nivolumab alone (26%). The median PFS was 7.4, 2.6, and 2.8 months, respectively, and the median OS was 15.3, 7.4, and 9.9 months, respectively. These study results support combining nivolumab and ipilimumab, with a preference for a higher dose of ipilimumab (3 mg/kg vs. 1 mg/kg).

The NABUCCO trial (NCT03387761) explored the possibility of combining nivolumab and ipilimumab in a neoadjuvant setting, administering 3 cycles before cystectomy [35]. Out of 24 patients, 46% exhibited a pathological complete response (pCR), and 58% showed no residual disease (pTisN0/pTaN0). The DUTRENEO trial employed a similar combination of anti-PD-L1 (durvalumab) and anti-CTLA-4 (tremelimumab) neoadjuvant therapy, administering 3 cycles before cystectomy, in contrast to the adjuvant setting in the DANUBE trial [36]. Patients who were classified as “hot” based on tumor inflammation scores derived from 18-gene interferon gamma signatures had a pCR of 34.8% with the immunotherapy combination. However, this did not represent a significant improvement over chemotherapy. These findings corroborate those from a previous study by Gao et al. [37] conducted on cisplatin-ineligible patients, where 2 cycles of durvalumab and tremelimumab resulted in an overall pCR of 31.7%.

The combination of ICIs with chemotherapy in a neoadjuvant setting shows potential. A phase II trial, which added pembrolizumab to a regimen of cisplatin and gemcitabine, demonstrated that 36% of the 39 patients with MIBC achieved pT0N0, and 56% achieved less than pT2N0 [38]. A similarly designed study, which included the addition of atezolizumab, found that 41% achieved pT0N0 and 69% achieved less than pT2N0 at the time of cystectomy. Notably, none of the patients with less than pT2N0 experienced a relapse at a median follow-up of 16.5 months [39].

Enfortumab vedotin, an antibody-drug conjugate, works by inhibiting nectin-4, a protein that is highly expressed in UC and is linked to tumor progression. The EV-301 trial demonstrated that this drug can improve OS to 12.9 months in patients who have not responded to treatment with PD-1 or PD-L1 inhibitors [40]. The FDA has approved the addition of pembrolizumab for use in advanced or metastatic UC patients who are ineligible for cisplatin-based chemotherapy, based on the results of the EV-103/KEYNOTE-869 trial (NCT03288545) [41]. In this phase II/
II multicenter study, an objective response was observed in 73.3% of patients, and a complete response in 15.6%, out of a total of 45 patients. The median OS was 26.1 months after a median of 9 cycles. The study also noted significant durability, with a median duration of 25.6 months. A phase III trial (NCT04223856) is currently in progress to compare the efficacy of this treatment to chemotherapy.

**BIOMARKERS FOR PATIENT SELECTION**

Given the aggressive nature and unfavorable clinical progression of most cases of UC, not all patients respond well to IO therapy. Many experience early recurrence and rapid disease progression. Currently, the FDA-approved urinary biomarkers for screening include the Bladder Tumor Antigen Assay (BTA-TRAK, BTA-stat) [42], nuclear matrix protein 22 (NMP22) [43], ImmunoCyt [44], and UroVysion FISH [45, 46]. These have shown promising sensitivity rates of 53%–87% and specificity of up to 77% in multiple meta-analyses. However, despite an increase in diagnostic accuracy with higher tumor grades and burdens, these screening methods have not been able to replace traditional cytology. They also lack utility or validation in IO settings. Therefore, clinical biomarkers for the predictive stratification of IO responders and non-responders are crucial for personalized medicine.

PD-L1 expression and TMB have been linked to improved OS in patients undergoing avelumab maintenance [47], and PD-L1 has also been utilized as a criterion for patient enrollment in early ICI monotherapy for those ineligible for cisplatin [48]. However, while patients with high PD-L1 expression often exhibit a favorable response, as evidenced by a high objective radiographic response rate, this does not necessarily equate to improved OS and is associated with significant heterogeneity [49]. Both patients with and without positive PD-L1 demonstrate a therapeutic response to ICI, but the absolute expression rates do not consistently correlate with treatment outcomes. Randomized trials involving first and second-line mono-ICI with pembrolizumab [4, 7], atezolizumab [8], and davalumab [12] have shown mixed results, with response rates as low as 20% even in PD-L1 positive patients, thus challenging the discriminatory role of PD-L1 in patient enrollment. This issue is further complicated by the lack of standardization and variability in the definition of PD-L1 positivity across clinical trials, an area that requires further clarification [50].

TMB quantifies the total number of genetic alterations in a tumor cell’s DNA, including point mutations, insertions, deletions, and rearrangements. It is typically expressed as the number of mutations per unit of DNA, such as mutations per megabase (Mb) or mutations per exome. TMB may be a more clinically relevant biomarker, particularly given the uniform approval of pembrolizumab for any solid tumors with over 10 mutations/Mb. An assessment of TMB in mUC treated with nivolumab found a strong correlation with improved OS (11.63 months vs. 5.72 months) and PFS (3.02 months vs. 1.91 months), as well as ORR (31.9% vs. 10.9%) for high TMB vs. low TMB, respectively [51]. A metaanalysis of ICIs in bladder cancer by Litchfield et al. [52] further supported these findings, identifying clonal TMB as the strongest predictor of ICI treatment response, followed closely by total TMB levels.

Microsatellite instability and gene expression profiling (GEP) have both been suggested as potential predictive biomarkers for ICI response. Somatic mutations in DNA damage repair (DDR) are associated with a higher TMB and can predict clinical progression following ICI treatment in UC and other histologically distinct cancers [52, 53]. However, the IMvigor210 study found that the clinical benefit of DDR was not independent of TMB [54], a finding echoed by the JAVELIN study. GEP, which measures genetic activity at the time of sampling, provides a more accurate representation of the dynamic tumor status and its microenvironment [55]. Robertson et al. [56] were able to identify 5 distinct GEP subtypes with varying responses to neoadjuvant ICI prior to cystectomy, noting the resistance effect of KDM5B. Similarly, the IMvigor210 and 130 trials found that increased expression of the transforming growth factor β ligand and its receptors correlated with poorer treatment response and prognosis [57, 58].

**FURTHER CONSIDERATIONS**

A critical concern with immunotherapy/ICI therapy is that, despite its clear oncological benefits and therapeutic efficacy, cost-effectiveness analyses have not been compelling
enough to recommend its use for all candidates [59]. Current socioeconomic constraints on healthcare have limited its use to advanced, metastatic diseases, and cost-benefit analyses comparing it to conventional chemotherapy and between different ICI agents have yielded mixed results. Utilizing data from KEYNOTE-045 [5] to compare pembrolizumab versus chemotherapy and IMvigor211 [60] for pembrolizumab versus atezolizumab, Slater et al. [61] reporting convincing evidence to support the economic benefit of ICIs over conventional therapy, with pembrolizumab patients gaining a mean of 1.33 life-years and 1.14 quality-adjusted life-years (QALY) at an increased cost of $106,299. The difference was more pronounced when compared to atezolizumab, with pembrolizumab reducing costs by over $26,000 while extending life by an average of 0.89 years. At a willingness-to-pay threshold of $100,000, pembrolizumab was cost-effective in 66% of cases compared to chemotherapy and in 100% of cases compared to atezolizumab. Similar results were found in Sweden [62] and United Kingdom [63], with an average survival gain of 1.66 years at a cost of €71924/QALY for pembrolizumab compared to chemotherapy regimens including paclitaxel, docetaxel, and vinflunine. For patients who cannot undergo cisplatin-based treatment, pembrolizumab remains a cost-effective therapy compared to the less effective alternative of carboplatin plus gemcitabine [64]. The KEYNOTE-057 trial for high-risk NMIBC led to FDA approval for the use of pembrolizumab for BCG-unresponsive populations in 2020 [28]; however, when compared to RC and salvage intravesical chemotherapy, there was little cost benefit, with pembrolizumab only becoming cost-effective after a cost reduction of over 93% [65]. No benefit was found for the use of ICIs in neoadjuvant settings for metastatic MIBC, with the exception of atezolizumab versus dose-dense methotrexate, vincristine, doxorubicin, and cisplatin [66]. Pembrolizumab required an 89% cost reduction compared to chemotherapy, suggesting that despite its survival benefits, the use of ICIs/immunotherapy may be limited by healthcare and insurance models, particularly for non-metastatic, localized diseases. One concern is the immune-related adverse effects (irAEs) that arise due to the mechanism of action of immunotherapy and ICIs. Tumor cells can evade immune surveillance by activating immune regulatory pathways that inhibit T-cell function and proliferation. By disrupting these interactions, ICIs enable cytotoxic T cells to attack tumors. However, immune checkpoint pathways also play a crucial role in homeostasis, and their dysregulation can lead to autoimmune diseases. Unlike molecularly targeted or cytotoxic agents, irAEs associated with ICIs can affect various organ systems and may occur at any time during or after treatment. The incidence varies among trials due to inconsistent definitions and reporting protocols. In trials involving PD-1/PD-L1 inhibitors for UC, approximately 15% of patients experienced irAEs that required corticosteroid treatment [67]. Systemic irAEs are common but generally well tolerated, with a relatively high rate of fatigue and headaches (up to 40%) and infusion-related reactions (up to 10%) with avelumab [3, 68]. Gastrointestinal toxicity is common but not necessarily more frequent than with chemotherapy, although hepatotoxicity can manifest in potentially severe forms [12]. Almost all clinical trials report skin complications such as rash and pruritis, with incidences up to 30% regardless of the agent dose [34]. Although combination ICIs do not necessarily increase risk, the DANUBE trial found that the combination of durvalumab and tremelimumab resulted in a higher incidence compared to durvalumab monotherapy (15%–22.9% vs. 7%–10.4%) [12]. More severe instances of irAEs include thyroid dysregulation and pneumonitis. The rate of hypothyroidism is significantly higher than that seen with chemotherapy, ranging from 6.4% to 13.0% with ICIs, as opposed to 1.2% with conventional gemcitabine and cisplatin chemotherapy [69]. Given that half of these cases result in irreversible damage necessitating lifelong replacement therapy, it is crucial to closely monitor thyroid function through blood tests, as symptoms may be easily mistaken for fatigue or lethargy. Respiratory distress, while less common, accounting for only around 4% of irAEs, has been linked to a high mortality rate [4, 34]. As the number of approved ICIs grows and more indications arise, it is expected that irAEs will become more prevalent. However, diagnosing irAEs can be challenging due to their varied clinical presentations, which can lead to delayed identification and missed opportunities for early intervention. Consequently, urologists should be vigilant for such clinical symptoms, ensuring prompt management and timely detection during immunotherapy/
ICl therapy.

**CONCLUSIONS**

Clinical trials and real-world evidence have shown that ICls can yield long-lasting responses and enhance survival rates in certain patients with UC. However, these treatments do not elicit the same response in all patients, and the identification of predictive biomarkers and patient characteristics remains a dynamic field of research. As evidenced by durvalumab [12] and atezolizumab [8], negative results from subsequent trials can lead to voluntary product withdrawals, thereby constantly altering the potential usage of these agents. Current research is focused on optimizing their application, pinpointing predictive biomarkers, and investigating innovative combinations with other treatments to further enhance patient outcomes for those with UC.

**NOTES**

- Conflicts of Interest: The authors have nothing to disclose.
- Funding/Support: This study was supported by the SNUBH research fund (2021-00031) and the National Research Foundation of Korea (NRF 2020R1A2C1100011).
- Author Contribution: Conceptualization: SHS, JJO; Data curation: SHS; Formal analysis: SHS; Funding acquisition: JJO; Methodology: SHS; Project administration: SHS, JJO; Visualization: SHS, JJO; Writing - original draft: SHS; Writing - review & editing: SHS, JJO.
- ORCID
  Sang Hun Song: https://orcid.org/0000-0003-3016-0032
  Jong Jin Oh: https://orcid.org/0000-0003-0448-5992

**REFERENCES**

open-label, phase 3 randomised controlled trial. Lancet 2018;391:748-57.
33. Rosenberg J, Sharma P, de Braud F, Basso U, Calvo E, Bono P, et al. Nivolumab (N) alone or in combination with ipilimumab (I) in patients (pts) with platinum-pretreated metastatic urothelial carcinoma (mUC), including the nivolumab 1 mg/kg+ ipilimumab 3 mg/kg expansion from CheckMate 032. Ann Oncol 2018;29:vii7.25.
34. Sharma P, Siefker-Radtke A, De Braud F, Basso U, Calvo E, Bono P, et al. 749P Nivolumab (N) alone or in combination with ipilimumab (I) in patients (pts) with platinum-pre-treated metastatic urothelial carcinoma (mUC): Extended


