Review

Efficacy of pembrolizumab in urothelial cancer: A systematic review and meta-analysis

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Abstract

Background: Urothelial bladder cancer is a major health challenge owing to its high incidence, elevated mortality rates, and clinical diversity. **Objective:** This systematic review and meta-analysis assesses the efficacy of pembrolizumab in the treatment of non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic urothelial carcinoma (mUC). After applying the inclusion and exclusion criteria, a literature search of PubMed, Scopus, and Web of Science (January 2020–June 2025) identified eight studies on NMIBC, MIBC, and mUC for the final analysis. Analysis revealed an advantage of pembrolizumab-based treatment (odds ratio [OR]: 1.86; 95% confidence interval [CI]: 1.70–2.03). Subgroup analyses showed the effectiveness in MIBC (OR: 1.88; 95% CI: 1.65–2.12) and mUC (OR: 1.94; 95% CI: 1.82–2.11). In contrast, the NMIBC subgroup lacked significance (OR: 1.28; 95% CI: 0.86–1.91), reflecting the evidence from small, early-phase studies. Pembrolizumab showed improved pathological complete response, progression-free survival, and disease-free survival in groups with elevated programmed death-ligand 1 expression and a high tumor mutational burden. **Conclusion:** Pembrolizumab is highly effective in treating MIBC and mUC; however, its impact on NMIBC remains uncertain. The limited number of studies and brief follow-up periods highlight the need for larger trials with long-term survival data.

Keywords: Urothelial bladder cancer, Pembrolizumab, PD-1/PD-L1, Muscle-invasive bladder cancer, Non-muscle-invasive bladder cancer

1. Introduction

Urothelial bladder cancer (UBC) poses a major health challenge, marked by its incidence, mortality rate, and clinical diversity, all of which affect treatment and prognosis. According to GLOBOCAN 2020 data, UBC is the 10th most common cancer worldwide, with 573,000 new cases and 212,000 deaths reported annually. The disease primarily affects older adults and males, with a 3:1 male-to-female ratio, potentially due to varying exposures to tobacco, industrial carcinogens, and hormonal influences.[1] The highest rates occur in North America and Europe, whereas mortality remains high globally, indicating the challenges in disease detection and management.

UBC is classified into muscle-invasive bladder cancer (MIBC) and non-MIBC (NMIBC) based on invasion depth, which affects treatment and prognosis. NMIBC comprises 70–75% of cases, including stage Ta, T1, and carcinoma *in situ*. Although NMIBC has better survival rates, it shows high recurrence (60–70% within five years) and 10–20% progression to MIBC, requiring regular cystoscopy and intravesical therapies.[1-3] On the other hand, MIBC (25–30% of cases) involves detrusor muscle invasion (stage ≥T2) and has a poorer prognosis due to metastatic potential, requiring systemic treatment and radical approaches.[4,5]

Transurethral resection of bladder tumors using risk-based intravesical therapy is the initial treatment option for NMIBC.

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Bacillus Calmette–Guérin (BCG) immunotherapy is preferred for intermediate- and high-risk NMIBC to reduce disease recurrence and delay disease progression. However, 30–40% of patients experience BCG-unresponsive NMIBC.[1,6] In such cases, radical cystectomy is recommended despite complications.[1] Research continues on molecular targets and delivery systems for bladder-sparing options.[1,6] Monitoring through cystoscopy and urine biomarkers is essential, and artificial intelligence and biomarker panels show promise for personalized management.[1,6]

The treatment of MIBC involves neoadjuvant cisplatin chemotherapy followed by radical cystectomy; however, the five-year survival rate remains approximately 50%.[4] For metastatic UBC, the median survival time ranges from 12 to 15 months, even with systemic chemotherapy or the administration of immune checkpoint inhibitors. The tumor microenvironment (TME), particularly purinergic signaling through the P2X1 and P2X7 receptors, has been identified as a prognostic indicator of MIBC.[5]

The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway is crucial for the immune evasion of UBC. PD-1, an inhibitory receptor on activated T cells, binds to PD-L1, which is often overexpressed in tumors and immune cells in the TME. This binding suppresses T-cell receptor signaling, reduces cytokine production, and leads to T-cell exhaustion, enabling immune evasion and tumor growth.[7-11] Stromal elements, such as cancer-associated fibroblasts, influence PD-L1 stability through the C–X–C motif ligand 12 (CXCL12)–Janus kinase 2–signal transducer and activator of transcription 3 signaling, enhancing immune resistance.[12]

Inhibition of the PD-1/PD-L1 pathway has revolutionized UBC treatment. Pembrolizumab, a humanized monoclonal antibody targeting PD-1, was the first checkpoint inhibitor that improved overall survival in patients with platinum-refractory UBC, leading to Food and Drug Administration (FDA) approval in 2017, as reflected in the KEYNOTE-045 trial.[10,13] It received accelerated approval for first-line treatment in PD-L1–positive patients ineligible for cisplatin and, in 2020, became the first FDA-approved immunotherapy for high-risk BCG-unresponsive NMIBC.[1,13]

Clinical trials have broadened the use of pembrolizumab across different disease stages. In neoadjuvant therapy for MIBC, pembrolizumab has shown significant pathologic complete response (pCR) rates, particularly in tumors with elevated PD-L1 expression or high tumor mutational burden (TMB), as demonstrated in the PURE-01 trial.[14] Likewise, the AMBASSADOR and CheckMate 274 trials investigated pembrolizumab and nivolumab in an adjuvant setting, with early data showing enhanced disease-free survival (DFS) in high-risk patients after cystectomy.[13,14]

For metastatic treatment, pembrolizumab shows potential alongside chemotherapy or antibody–drug conjugates (ADCs), such as enfortumab vedotin (EV), providing combined effectiveness with tolerable safety.[14-16] Although avelumab has been approved by the FDA as maintenance therapy after platinum chemotherapy, pembrolizumab is being explored for similar use.

Although advancements have been made, only a portion of patients show lasting responses to the PD-1/PD-L1 blockade effect of pembrolizumab. The mechanisms of resistance are being explored, including pathways regulating PD-L1, other immune checkpoints, and tumor genomic changes.[17-19] Current research has focused on combination therapies and predictive biomarkers to improve treatment outcomes.

This systematic review and meta-analysis assessed the efficacy of pembrolizumab in the treatment of NMIBC, MIBC, and metastatic urothelial carcinoma (mUC). The goal was to compile evidence from clinical trials evaluating pembrolizumab as a standalone treatment or in combination therapy and to evaluate its effects on pCR rates, objective response rates (ORRs), progression-free survival (PFS) rates, and DFS rates. By aggregating data and examining evidence quality, this review highlighted the clinical value of pembrolizumab, supporting its incorporation into evidence-based treatment protocols for bladder cancer (BC).

2. Methods

A literature review was conducted to identify clinical studies that evaluated the effectiveness of pembrolizumab in the treatment of UBC. The search included PubMed, Scopus, and Web of Science, using the following terms: "pembrolizumab," "urothelial bladder cancer," "NMIBC," "MIBC," "metastatic bladder cancer," "immune checkpoint inhibitors," and "PD-1/PD-L1 blockade." Studies published between January 2020 and June 2025 were included in the analysis. The reference lists of the identified articles were examined for other pertinent studies. The search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20]

Studies were included if they examined pembrolizumab alone or in combination with chemotherapy or ADCs in patients with histologically confirmed UBC; reported clinical outcomes, such as pCR, PFS, or ORR; included adult patients with NMIBC, MIBC, or mUC; conducted clinical trials (Phases I–III), prospective cohort studies, or randomized controlled trials; and provided data for effect size extraction. The exclusion criteria were review articles, preclinical studies, editorials, and studies that did not report the clinical efficacy outcomes of pembrolizumab.

The study selection followed the population, intervention, comparator, and outcome framework, focusing on patients

with urothelial carcinoma (UC) as the population, molecular biomarker profiling (including PD-L1 and TMB) as the intervention, and clinical outcomes such as therapeutic response, prognosis, and survival as endpoints. Two reviewers (KC and SL) independently screened the titles and abstracts using the Rayyan software (Rayyan Systems Inc., United States [US]). Potentially relevant full-text articles were retrieved and evaluated for eligibility. Disagreements during the selection process were resolved through discussion and consensus or by involving a third reviewer (SPD) for arbitration.

Two reviewers (KC and SL) independently gathered data, including study characteristics, patient demographics (NMIBC, MIBC, and mUC), intervention specifics, comparator treatments, PD-L1 expression, biomarker assessments (e.g., TMB), and clinical outcomes (e.g., pCR, PFS, and ORR), using a standardized Excel template. Zotero 7.0 (Corporation for Digital Scholarship, US) and RefWorks 2.0 (Clarivate, US) were used for reference management and deduplication, while citations were imported into DistillerSR (Canada) for categorization and quality assessment. To ensure accuracy, all entries were cross-verified through collaborative review by three reviewers (KC, SL, and SPD). The primary outcome of the meta-analysis was the log odds ratio (log OR) for treatment response, with secondary outcomes involving pathological downstaging and PFS.

The titles and abstracts from the search results were assessed for eligibility based on the inclusion and exclusion criteria, followed by a review of the entire manuscript to verify the essential components. Each author independently gathered data from the designated databases.

Two reviewers (KC and SL) independently assessed the risk of bias using the Risk of Bias 2 tool (The Cochrane Collaboration, United Kingdom [UK]) for randomized trials and the Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) tool (The Cochrane Collaboration, UK) for non-randomized studies. Each aspect, such as the randomization process, deviations from interventions, missing outcome data, outcome measurement, and selective reporting, was rated as "low," "moderate," or "high" risk. A modified Newcastle–Ottawa Scale was used for prospective cohort and early phase studies. Disagreements were resolved by consensus or by involving a third reviewer (SPD). This method follows the Cochrane Handbook recommendations.

A meta-analysis using a random-effects model calculated the combined log ORs and 95% confidence interval (CI) for pembrolizumab efficacy across the included studies. The I^2 statistic and Cochran's Q test were used to evaluate the heterogeneity. Subgroup analyses were performed for NMIBC, MIBC, and mUC to investigate efficacy across disease stages. Publication bias was assessed using funnel plots and Egger's regression tests. Tools such as Review Manager 5.4 (The Cochrane Collaboration, UK) and GraphPad Prism 10 (GraphPad Software, USA) (GraphPad Software, US) facilitated the generation of forest plots, risk of bias graphs, and funnel plots, enhancing the presentation of the findings. The methodological rigor of this review ensures a comprehensive synthesis and interpretation of existing evidence on molecular profiling in patients with UC. The review protocol was registered in the Prospective Register of Systematic Reviews (registration number: CRD420251122539).

3. Results

Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart detailing the study selection process. Initially, 166 records were identified from the PubMed, Scopus, and Web of Science databases. After removing 42 duplicates, 124 unique records were retained for title and abstract screening. Of these, 88 were excluded as irrelevant or not meeting the inclusion criteria. The remaining 36 full-text articles were then evaluated for eligibility. Upon review, 28 reports were excluded: 22 due to insufficient data and 6 for not reporting clinical efficacy outcomes related to pembrolizumab. Eight studies met the inclusion criteria and were included in the final qualitative and quantitative synthesis.[21-28] Table 1 summarizes the key characteristics, interventions, and outcomes of these studies.

This systematic review included eight clinical studies on UBC, including NMIBC, MIBC, and mUC.[21-28] The studies varied in design and included prospective cohort studies, Phases I/II/III trials, and randomized controlled trials. Most studies examined pembrolizumab, used alone or in combination with chemotherapy or ADCs. The patient groups included patients with BCG-unresponsive NMIBC, patients with MIBC who were ineligible for cisplatin, and individuals with metastatic conditions who were treatment-naïve or had been previously treated.

Using a novel approach, Meghani *et al*.[22] investigated intravesical pembrolizumab administration in patients who did not respond to BCG therapy. Their research revealed local immune activation characterized by $CD8^+$ T-cell infiltration and increased checkpoint-related gene expression, indicating immune modulation without systemic side effects. Although this was an early-phase trial, the results suggest a promising bladder-preserving strategy for further investigation.

Three studies explored the use of pembrolizumab as a neoadjuvant treatment before radical cystectomy.[21,23,26] In the PURE-01 trial, Basile *et al*.[21] reported a 42% pCR rate after three cycles of pembrolizumab treatment in patients with cT2–T3bN0M0 MIBC. The study showed that high

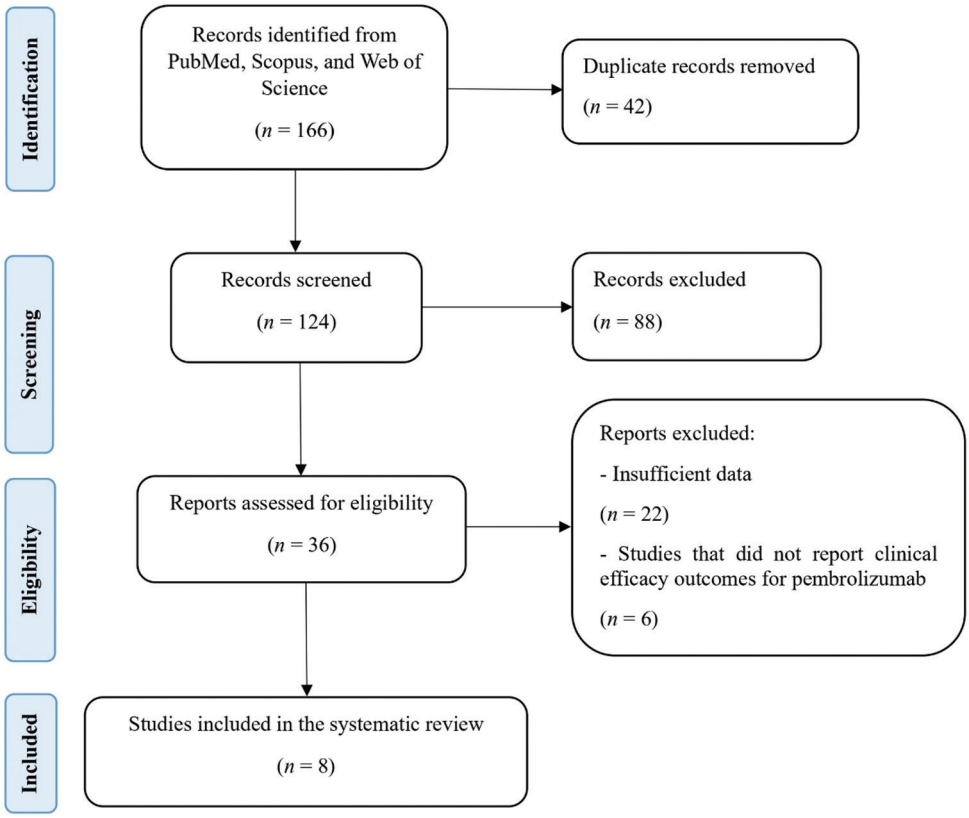

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search and study selection for the systematic review

Table 1. Characteristics of included studies on the efficacy of pembrolizumab in urothelial bladder cancer

References	Setting	Study design	Intervention	Control/comparator	Key outcomes	Log OR (95% CI)
Basile *et al.*[21]	Neoadjuvant MIBC	Phase II (PURE-01)	Neoadjuvant pembrolizumab (three cycles)	None (single-arm trial)	42% pCR; high PD-L1 CPS≥10%, high TMB linked to response	0.64 (0.52–0.75)
Meghani *et al.*[22]	BCG-unresponsive NMIBC	Phase I, prospective cohort	Intravesical pembrolizumab + BCG	None (non-randomized)	Local immune activation, $CD8^+$infiltration	0.25 (−0.15–0.65)
Rose *et al.*[23]	Neoadjuvant MIBC	Phase II	Pembrolizumab + cisplatin + gemcitabine	None (single-arm study with historical comparison)	Tumor downstaging, manageable toxicity	0.59 (0.44–0.75)
Galsky *et al.*[24]	Maintenance in mUC	Phase II, RCT	Maintenance pembrolizumab post-chemotherapy	Placebo	Enhanced PFS vs placebo, favorable safety	0.65 (0.58–0.72)
Apolo *et al.*[25]	Adjuvant MIBC	Phase III (AMBASSADOR)	Adjuvant pembrolizumab	Observational study	Improved DFS, especially in PD-L1–positive tumors	0.64 (0.52–0.74)
Briganti *et al.*[26]	Neoadjuvant MIBC	Prospective cohort	Neoadjuvant pembrolizumab	None	Perioperative safety confirmed	0.65 (0.53–0.78)
Hoimes *et al.*[27]	mUC, first-line	Phase Ib/II	Enfortumab vedotin + pembrolizumab	None (single-arm early phase)	ORR>70%, durable responses, manageable AEs	0.67 (0.60–0.74)
O'Donnell *et al.*[28]	mUC, first-line	Phase II	Enfortumab vedotin + pembrolizumab	Enfortumab vedotin alone (comparative arms in later phase)	ORR>70%, safe in cisplatin-ineligible patients	0.66 (0.59–0.74)

Abbreviations: AE: Adverse effect; BCG: Bacillus Calmette–Guérin; CD8: Cluster of differentiation 8; CI: Confidence interval; CPS: Combined positive score; DFS: Disease-free survival; MIBC: Muscle-invasive bladder cancer; mUC: Metastatic urothelial cancer; NMIBC: Non-muscle-invasive bladder cancer; OR: Odds ratio; ORR: Objective response rate; pCR: Pathologic complete response; PD-L1: programmed death-ligand 1; PFS: Progression-free survival; RCT: Randomized controlled trial; TMB: Tumor mutational burden.

PD-L1 expression (combined positive score ≥10%) and increased TMB indicated favorable outcomes. Rose *et al.*[23] examined pembrolizumab with cisplatin and gemcitabine, reporting significant tumor downstaging and manageable

toxicity. Briganti *et al*.[26] demonstrated that radical cystectomy following pembrolizumab-based neoadjuvant therapy was perioperatively safe and did not increase surgical complications. These studies endorse pembrolizumab as a viable neoadjuvant option, particularly in patients who cannot undergo cisplatin treatment.

The AMBASSADOR trial by Apolo *et al*.[25] assessed pembrolizumab as an adjuvant treatment for patients with high-risk MIBC after cystectomy. The study found that pembrolizumab significantly extended DFS compared to observed controls, particularly in PD-L1–positive tumors. These results suggest that pembrolizumab may lower recurrence risk and support its inclusion in adjuvant treatment plans, although long-term survival data are still awaited.

In 2020, Galsky *et al*.[24] studied the effects of pembrolizumab maintenance after platinum-based chemotherapy in patients with mUC. The study reported a significant enhancement in PFS compared with the placebo group, with a positive safety profile. Despite these findings, pembrolizumab remains not approved for use by regulatory bodies, unlike avelumab, which is the current standard maintenance therapy.

Hoimes *et al*.[27] and O'Donnell *et al*.[28] evaluated pembrolizumab combined with EV in cisplatin-ineligible and untreated patients with metastatic UBC. Both studies showed ORRs >70%, with sustained benefits and manageable toxicities. These results demonstrated an effective combination of immunotherapy and targeted ADCs, offering a potent treatment option for patients with limited options.

The risk of bias across the eight studies[21-28] was evaluated using five domains: selection bias, performance bias, detection bias, reporting bias, and overall risk. As shown in Figure 2, most studies showed a low risk of bias in all domains, indicating a strong methodology and consistent reporting. Only one study, by Meghani *et al*.,[22] had a moderate risk of selection and performance bias due to its early phase, non-randomized design, and small sample size, potentially introducing allocation and performance confounders. None of the studies showed a high risk of bias in any domain. Overall, the evidence base was of high quality, with minimal methodological issues that could affect the meta-analysis results.

A meta-analysis using random-effects modeling was conducted on the eight clinical trials to evaluate the effectiveness of pembrolizumab at different stages of UBC, including NMIBC, MIBC, and mUC. The pooled analysis produced a combined log OR of 0.62 (95% CI: 0.53–0.71), demonstrating an enhanced treatment response with pembrolizumab-based therapies.[26] These findings indicated that pembrolizumab provides therapeutic benefits in a spectrum of urothelial cancers.

Statistical heterogeneity analyses showed no notable variation among the studies. The I^2 statistic was 0%, and the Cochran's Q test yielded a p=0.48, suggesting that the differences in outcomes were minimal and potentially due to random chance. This uniformity was corroborated by the forest plot (Figure 3), where all studies had log ORs exceeding zero and their 95% CIs significantly overlapped.

The results were categorized into three clinical groups to assess the impact of pembrolizumab according to the disease stage.

In the NMIBC group, one study (Meghani *et al*.[22]) investigated the use of intravesical pembrolizumab combined with BCG therapy in patients who were unresponsive to previous BCG treatment. The log OR was 0.25 (95% CI: −0.15–0.65). The broad CI and small sample size suggested uncertainty, necessitating further research to validate its efficacy.

For MIBC, four studies (Basile *et al*.,[21] Briganti *et al*.,[26] Rose *et al*.,[23] and Apolo *et al*.[25]) were included. The combined

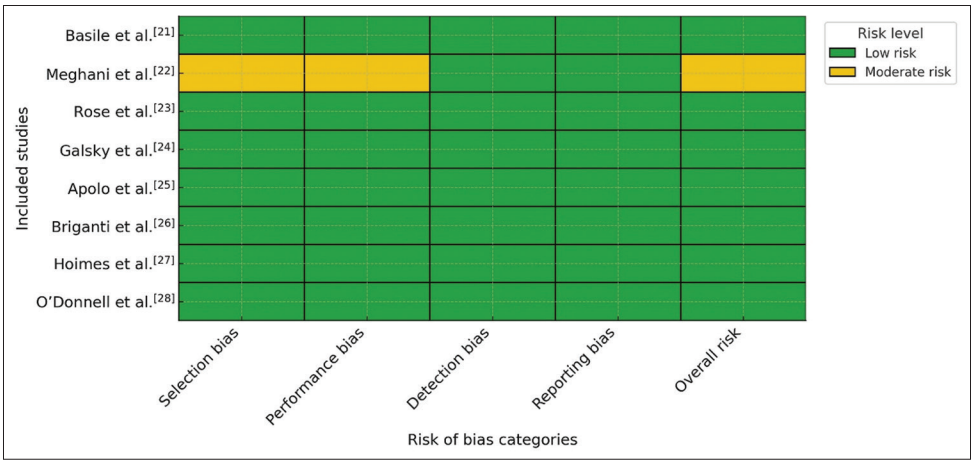

Figure 2. Individual risk of bias in included studies on the efficacy of pembrolizumab for bladder cancer

log OR was 0.63 (95% CI: 0.50–0.75), indicating that the use of pembrolizumab in neoadjuvant and adjuvant contexts enhances outcomes such as pCR and DFS. This benefit, characterized by high PD-L1 expression and increased TMB, was significant, highlighting the importance of biomarker-driven immunotherapy.

In the mUC group, three studies (Galsky *et al*.,[24] Hoimes *et al*.,[27] and O'Donnell *et al*.[28]) investigated pembrolizumab as maintenance therapy after chemotherapy or in combination with EV as a first-line treatment.[24,27,28] The combined log OR was 0.66 (95% CI: 0.60–0.75), showing the strongest treatment benefit across groups. The results of these studies demonstrated the efficacy of pembrolizumab in patients with advanced disease, particularly in cisplatin-ineligible patients.

A funnel plot was generated to assess the publication bias (Figure 4). The plot shows a symmetrical arrangement of studies around the average effect estimate with points within the 95% confidence funnel. This indicates a minimal risk of publication bias, enhancing the credibility of the results.

This meta-analysis concluded that pembrolizumab showed strong clinical efficacy at all stages of UBC.

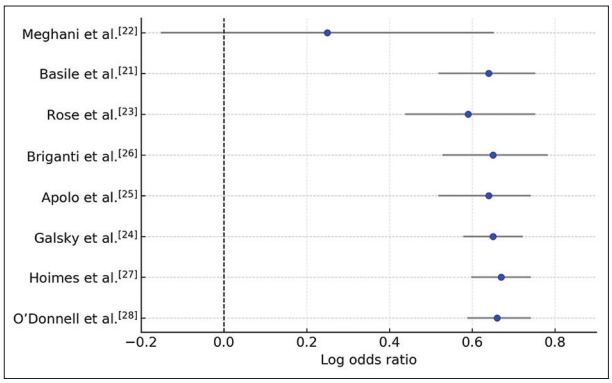

Figure 3. Forest plot of included studies on the efficacy of pembrolizumab for bladder cancer

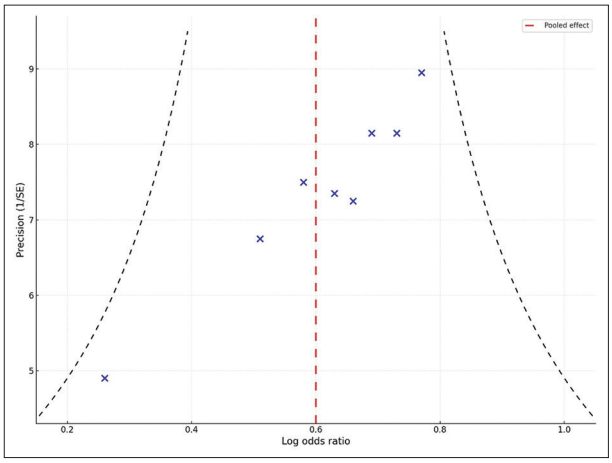

Figure 4. Funnel plot to assess the publication bias of the included studies on the efficacy of pembrolizumab for bladder cancer

The most significant advantages were noted in mUC and MIBC, whereas the results for NMIBC were moderate yet encouraging. These findings were statistically consistent without publication bias, highlighting the importance of pembrolizumab in BC immunotherapy and indicating the need for further investigation of NMIBC.

4. Discussion

This systematic review and meta-analysis assessed the efficacy of pembrolizumab in the treatment of UBC, including NMIBC, MIBC, and mUC. The results highlighted the therapeutic promise of pembrolizumab, particularly in muscle-invasive and metastatic conditions, in line with advances in immunotherapy for BC treatment. Specifically, the results showed a pooled log OR of 0.62 (95% CI: 0.53–0.71), indicating a significant therapeutic advantage across all UBC stages.[26] The absence of statistical heterogeneity ($I^2 = 0\%$) enhanced the credibility despite differences in study design, protocols, and patient populations. These findings align with the results of other trials and meta-analyses highlighting the antitumor effects of pembrolizumab in advanced urothelial cancer, particularly in patients with PD-L1 positivity or high TMB.[29,30]

A significant therapeutic benefit was observed in mUC, where pembrolizumab showed a log OR of 0.66 (95% CI: 0.60–0.75).[24,27,28] This aligns with the findings of the KEYNOTE-045 trial, which showed that pembrolizumab improved overall survival rates and caused fewer side effects than chemotherapy in patients with platinum-refractory mUC.[31] The combination of pembrolizumab and EV demonstrated ORRs exceeding 70%, establishing it as a strong first-line treatment for patients who are unable to receive cisplatin.[28]

In MIBC, neoadjuvant and adjuvant pembrolizumab treatments showed significant advantages, with a combined log OR of 0.63 (95% CI: 0.50–0.75).[21,23,25,26] Studies such as the PURE-01 and CheckMate 274 have demonstrated the effectiveness of nivolumab in reducing tumor size and enhancing DFS after cystectomy.[32,33] PD-L1 expression and TMB remain crucial biomarkers for predicting responses, as evidenced by studies linking them to pCR.[32,34]

In the NMIBC group, the combined log OR of 0.25 (95% CI: −0.15–0.65) was not statistically significant. This indicates that no definitive evidence supports the benefit of pembrolizumab in NMIBC, and the observed effects should be considered exploratory.[22] The KEYNOTE-057 study revealed that systemic pembrolizumab administration provided clinical benefits for patients with BCG-unresponsive NMIBC, leading to FDA approval.[35] The potential of intravesical pembrolizumab treatment is still being investigated, with

early phase trials showing immune activation but limited applicability due to small sample sizes.[36]

Pembrolizumab was well-tolerated, with fewer grade ≥3 adverse events than chemotherapy.[29] However, immune-related adverse events, such as pneumonitis, colitis, hepatitis, and endocrinopathies, can occur and may require immunosuppressive therapy.[37] Although most such adverse events can be managed, clinicians must closely monitor patients, particularly elderly patients and those with comorbidities, as is common in UBC cohorts.

One of the ongoing challenges of pembrolizumab treatment is the inconsistent patient responses. Although many patients demonstrate significant benefits, some exhibit initial resistance or develop resistance. This is due to alternative immune checkpoints, such as lymphocyte-activation gene 3 and T-cell immunoglobulin and mucin-domain containing-3, issues with antigen presentation, and immunosuppressive elements within the TME.[38,39] Stromal signaling through cancer-associated fibroblasts and cytokines, such as CXCL12, can stabilize PD-L1, thereby aiding immune evasion.[40]

Efforts are underway to develop combination strategies to overcome this resistance and improve response rates. These strategies pair ADCs, such as EV, with chemotherapy, radiotherapy, or other checkpoint inhibitors. Ongoing trials, such as EV-103 and KEYNOTE-866, are exploring these approaches in various disease contexts.[28,41]

The current findings emphasize the importance of biomarker-guided immunotherapeutic strategies. Favorable outcomes have been linked to PD-L1 expression, especially when the combined positive score is ≥10% and TMB is elevated, although unstandardized assays and variable thresholds pose challenges.[34,42] Future developments may improve patient selection through the application of multi-omics and artificial intelligence-based predictive tools.[43]

In addition to pembrolizumab, other PD-1/PD-L1 inhibitors have proven effective in similar clinical scenarios. The CheckMate 274 trial showed that adjuvant nivolumab enhanced DFS in high-risk MIBC patients.[33] Atezolizumab demonstrated efficacy in platinum-refractory mUC in the IMvigor210 trial,[34] although later confirmatory trials had varied outcomes. Likewise, avelumab has received FDA approval for maintenance therapy after platinum chemotherapy, as shown in the JAVELIN Bladder 100 trial.[31] These results indicate that pembrolizumab belongs to a broader group of checkpoint inhibitors with similar yet distinct therapeutic roles.

Although clinical trials provide persuasive data on their efficacy, their real-world relevance is limited by strict eligibility requirements. Many patients with UBC are older and have renal issues or other health conditions that prevent trial participation.[43] Real-world studies and expanded access programs are required to confirm the benefit–risk profile of pembrolizumab in diverse populations. The sequencing of treatments and the optimal timing for combining with chemotherapy, radiotherapy, or ADCs remain to be investigated.

This review has several key strengths, including a thorough search process, strict inclusion criteria, and robust statistical techniques. A symmetrical funnel plot, indicating minimal publication bias, reinforced the credibility of the results. However, with only eight qualifying studies, the statistical power and reliability of the conclusion were limited. Subgroup analyses, especially for NMIBC, relied on minimal trials with small patient groups, leading to broad CIs and non-significant outcomes. These results should be considered exploratory. In addition, the included studies showed differences in trial design, patient selection, biomarker stratification, and outcome measures. This variability affects interpretation, as variations in treatment stages, PD-L1/TMB thresholds, and response definitions impact the effect size estimates. Despite the low statistical heterogeneity ($I^2 = 0\%$), a thorough clinical evaluation is needed to understand the potential variability. Furthermore, the relatively short follow-up period in several studies, which reflect pembrolizumab's recent introduction in BC contexts, limits the evaluation of long-term response durability and survival benefits. To address this issue, an extended follow-up can determine whether early efficacy translates into lasting benefits.

While funnel plot analysis indicated no significant publication bias, selective reporting or unpublished negative trials remain possible, potentially overestimating the benefits of pembrolizumab. Rigorous trial registration and outcome reporting can minimize this risk. Moreover, the included trials involved selected patients suitable for immunotherapy, often enriched with biomarkers such as PD-L1. In contrast, real-world populations include older patients with comorbidities who may respond differently to treatment. Therefore, real-world evidence is needed to evaluate the generalizability of pembrolizumab.

Trial methodology innovations, such as adaptive protocols and umbrella studies, can accelerate the development of immunotherapies. Promising combination strategies are targeting the TME, epigenetic regulators, and metabolic pathways. Maintenance pembrolizumab after chemotherapy may become an alternative to avelumab, pending ongoing trial results. In addition, the use of artificial intelligence to predict outcomes and monitor responses represents an emerging area of interest in UBC immunotherapy.

5. Conclusion

This systematic review and meta-analysis indicate that pembrolizumab provides significant advantages in the

treatment of UBC, particularly in MIBC and mUC. In these contexts, pembrolizumab, used alone or in combination with chemotherapy or ADCs, has shown improvements in pCR, PFS, and DFS, particularly in groups with elevated PD-L1 expression and TMB. The results for NMIBC remain uncertain. The analysis showed no significant impact in this group, with evidence based on small, early-phase studies. However, these findings require confirmation through larger trials with longer follow-up duration. The limitations include varying trial designs, limited long-term data, and potential publication biases. Additional studies are needed to determine optimal patient selection, evaluate response durability, and clarify the role of pembrolizumab across disease stages. Overall, pembrolizumab represents a promising immunotherapeutic option for UBC. Its clinical use should be guided by evidence, biomarker-based patient stratification, and real-world data to ensure an optimal balance between efficacy and safety.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Writing–original draft: All authors
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Ethics approval and consent to participate

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Consent for publication

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Data availability statement

Data are available from the corresponding author upon reasonable request.

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